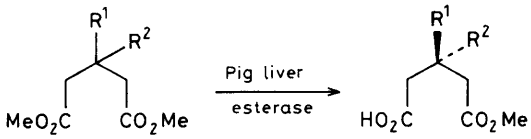
Preparations of Chiral δ-Lactones *via* Enantiotopically Specific Pig Liver Esterase-catalysed Hydrolyses of 3-Substituted Glutaric Acid Diesters

Christopher J. Francis and J. Bryan Jones*

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

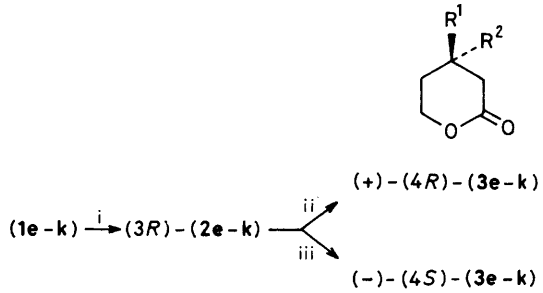
Pig liver esterase-catalysed hydrolyses of 3-monosubstituted glutaric acid diesters are *pro-S* enantiotopically specific for a broad range of C-3 substituents and permit either enantiomer of the corresponding 3-substituted valerolactones of 100% e.e. to be readily prepared.

The ability of enzymes to discriminate between enantiotopic groups attached to a prochiral centre has been recognised for many years.[1] 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,[2—9] 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.[3—9] 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,[4,9] negamycin,[5] verrucarinic acid,[7] and pimaricin fragments.[8] 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) (2)

a; R^1 = Me, R^2 = OH
b; R^1 = NH_2, R^2 = H
c; R^1 = CH_2Ph, R^2 = Me (malonate series)
d; R^1 = H, R^2 = OH
e; R^1 = Me, R^2 = H
f; R^1 = Et, R^2 = H
g; R^1 = Pr, R^2 = H
h; R^1 = $CHMe_2$, R^2 = H
i; R^1 = cyclohexyl, R^2 = H
j; R^1 = Ph, R^2 = H
k; R^1 = CH_2Ph, R^2 = H



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

Table 1. Results of reactions shown in Scheme 1.[a]

(1)	Yield of (2),%	Yield of (+)-(4*R*)-(3),%	Yield of (−)-(4*S*)-(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

[a] All lactones formed in > 99% e.e.

glutarate diester substrates. We now report that P.L.E.-catalysed hydrolyses of (**1**) → (**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.†

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

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,[4,7] optically pure products are obtained provided the pH of the reaction mixture is kept ≤7.

† 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.

‡ 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.[14] This P.L.E.-based method is far superior to previous alcohol dehydrogenase-dependent routes[2,3] 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**).[4,9] With one of two C-3 substituents large, as in (**1c**), the enantiotopic specificity largely disappears.[6]

We thank the Natural Sciences and Engineering Research Council of Canada for support.

Received, 2nd December 1983; Com. 1569

References

1 R. Bentley, 'Molecular Asymmetry in Biology,' vol. 1, Academic Press, New York, 1970; W. L. Alworth, 'Stereochemistry and its Application in Biochemistry,' Wiley–Interscience, New York, 1972.
2 C. Bally and F. Leuthardt, *Helv. Chim. Acta*, 1970, **53**, 732; R. A. Johnson, M. E. Hare, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, 1970, **35**, 622; R. A. Johnson, C. M. Hall, W. C. Krueger, and H. C. Murray, *Bioorg. Chem.*, 1973, **2**, 99; C. T. Goodhue and J. R. Schaeffer, *Biotechnol. Bioeng.*, 1971, **13**, 203; H. Ohta, H. Tetsukawa, and N. Noto, *J. Org. Chem.*, 1982, **47**, 2400; A. M. Klibanov, B. N. Alberti, and M. A. Marletta, *Biochem. Biophys. Res. Commun.*, 1982, **108**, 804; D. R. Dodds and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, 1982, 1080; M. Nakazaki, H. Chikamatsu, and M. Taniguchi, *Chem. Lett.*, 1982, 1761; D. W. Brooks, P. G. Grothuis, and W. L. Irwin, *J. Org. Chem.*, 1982, **47**, 2820.
3 A. J. Irwin and J. B. Jones, *J. Am. Chem. Soc.*, 1977, **99**, 556; J. B. Jones and K. P. Lok, *Can. J. Chem.*, 1979, **57**, 1025; A. J. Irwin, K. P. Lok, K. W-C. Huang, and J. B. Jones, *J. Chem. Soc., Perkin Trans.* 1, 1978, 1636.
4 F-C. Huang, L. F. H. Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi, and C. R. Eck, *J. Am. Chem. Soc.*, 1975, **97**, 4144; C-S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *ibid.*, 1982, **104**, 7294.
5 M. Ohno, S. Kobayashi, T. Iimori, Y.-F. Wang, and T. Izawa, *J. Am. Chem. Soc.*, 1981, **103**, 2405.
6 S. Iriuchijima, K. Hasegawa, and G. Tsuchihashi, *Agric. Biol. Chem.*, 1982, **46**, 1907.
7 P. Mohr, M. Tori, P. Grossen, P. Herold, and C. Tamm, *Helv. Chim. Acta*, 1982, **65**, 1412; P. Herold, P. Mohr, and C. Tamm, *ibid.*, 1983, **66**, 744.
8 D. W. Brooks and J. T. Palmer, *Tetrahedron Lett.*, 1983, **24**, 3059.
9 W. K. Wilson, S. B. Baca, Y. J. Barber, J. J. Scallen, and C. J. Morrow, *J. Org. Chem.*, 1983, **48**, 3960.
10 H. Brockmann and T. Reschke, *Tetrahedron Lett.*, 1968, **27**, 3167; Y. Naoshi, M. Yamaguchi, M. Kawai, L. Ichimoto, and H. Ueda, *Agric. Biol. Chem.*, 1974, **38**, 2273; S. Sahav and G. Sircar, *J. Chem. Soc.*, 1928, 54; G. P. Schiemenz and H. Englehard, *Chem. Ber.*, 1962, **95**, 195.
11 K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 492; C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, *J. Org. Chem.*, 1974, **39**, 3052.
12 J. W. Cornforth, R. H. Cornforth, G. Popjak, and L. Yengoyan, *J. Biol. Chem.*, 1966, **241**, 3970.
13 G. Saucy, R. Borer, D. P. Trullinger, J. B. Jones, and K. P. Lok, *J. Org. Chem.*, 1977, **42**, 3206.
14 A. Fischli in 'Modern Synthetic Methods,' vol. 2, ed. R. Scheffold, Salle/Sauerlander, Frankfurt, 1980, p. 269.