Highly Enantioselective Route to (*R*)-Proline Derivatives *via* Enzyme Catalysed Hydrolysis of *cis*-*N*-Benzyl-2,5-bismethoxycarbonylpyrrolidine in an Aqueous Dimethyl Sulphoxide Medium

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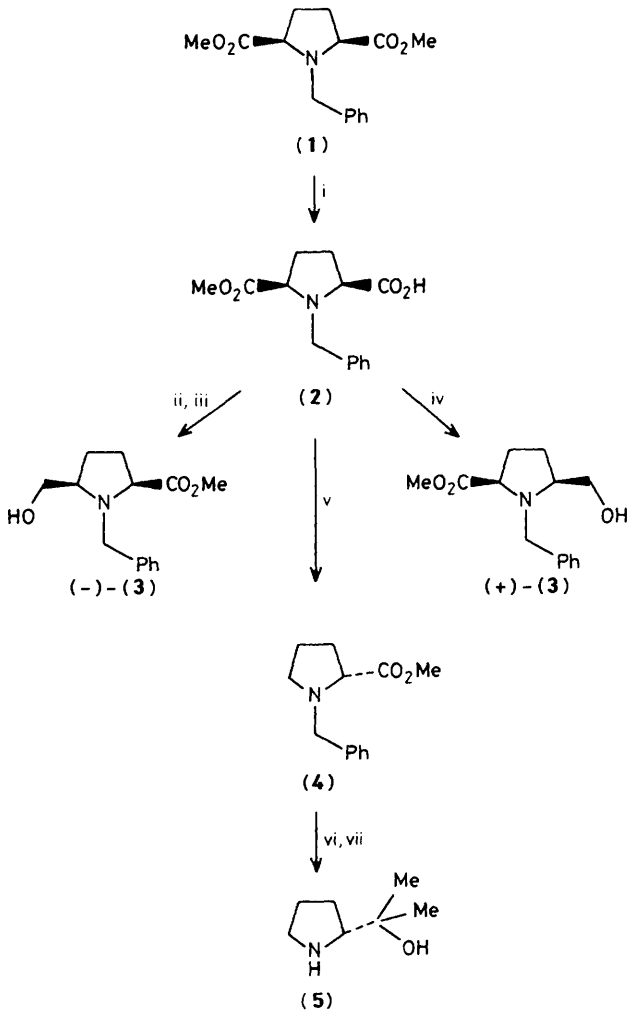
Pig liver esterase catalysed hydrolysis of diester (**1**) with dimethyl sulphoxide as cosolvent in buffered solutions gave optically pure monoester (**2**) which was further transformed to the (*R*)-proline related ester (**4**) by radical decarboxylation.

Enzyme catalysed hydrolysis of symmetrical diesters as an effective method of producing many interesting optically active compounds on a practical scale is currently under intensive investigation.[1] (2*S*,5*R*)-*N*-Benzyl-5-methoxycarbonylproline (**2**) should have significant potential as a starting material for the preparation of pyrrolidine alkaloids (*e.g.* ant signal substances[2]) and has been considered as a chiral synthon candidate for use in the synthesis of carbapenem antibiotics. In this context Ohno *et al.*[3] recently reported the pig liver esterase (PLE) catalysed hydrolysis of the readily available *meso* diester (**1**)[4] giving (**2**) in 80% enantiomeric excess (e.e.).

In this communication we describe the synthesis of the optically pure monoester (**2**) employing dimethyl sulphoxide (DMSO) as cosolvent in the enzymatic hydrolysis of (**1**).† The

† Several related pyrrolidine and piperidine diester substrates have been subjected to this hydrolysis. Our results with respect to changes in reaction conditions *etc.* will be presented in a forthcoming full paper.



Scheme 1. *Reagents and conditions:* i, PLE, DMSO–H_2O, pH 7.5; ii, LiOAc, $LiBH_4$–tetrahydrofuran (THF); iii, MeOH/H^+; iv, BH_3–THF; v, isobutyl chlorocarbonate, *N*-methylmorpholine, *N*-hydroxypyridine-2-thione, Et_3N, t-butyl thiol, irr. 300 W; vi, MeMgI; vii, H_2/Pd–C, MeOH.

dramatic influence of DMSO on enantioselectivity in the PLE-catalysed hydrolysis of dialkylated propanedioic acid dimethyl esters[5] and other diesters[6] has been shown in previous studies.

A DMSO concentration of 25% in the reaction medium‡ proved to give an enantiospecific hydrolysis of diester (**1**) (Table 1, entry 3). The chiral half-ester (**2**) was obtained in 39% chemical yield and 100% e.e. as directly determined from its ^1H n.m.r. spectrum in the presence of enantiomerically pure (*R*)-(+)-1-phenylethylamine.[7] Further experimental work to improve and explain the moderate chemical yield is in progress.

In order to demonstrate the usefulness of the monoester (**2**) as a versatile source of optically active *cis*-2,5-bifunctionalized pyrrolidines it was selectively transformed to either enantiomer of *N*-benzyl-*cis*-5-methoxycarbonylprolinol [*i.e.* (−)-(**3**) and (+)-(**3**)]§ (Scheme 1). Furthermore we have found (**2**) to be a valuable and general entry to (*R*)-proline derivatives through radical decarboxylation[8] to the ester (**4**) (46% yield). No racemisation occurs in this process as was shown by decarboxylation of monoester (**2**) to (**4**) of the same e.e. The optical purity of (**4**) was determined by ^1H n.m.r. spectroscopy in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$]. Racemic (**4**) required for this study was produced by treatment of (*S*)-(**4**) [derived from (*S*)-proline] with NaOMe.

The (*R*)-enantiomer of the crystalline aminol (**5**) (m.p. 36—38 °C) is thus now available *via* Grignard reaction of (**4**) with MeMgI followed by hydrogenation. The (*S*)-enantiomer of this interesting chiral auxiliary[9] has been conveniently prepared in four steps from (*S*)-proline *via* (*S*)-(**4**) (55% overall yield).

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Table 1. Optical purity of monoester (**2**) obtained by pig liver esterase catalysed hydrolysis of diester (**1**).‡

Entry	% DMSO	% e.e.[a]
1	0	17
2	10	61
3	25	100
4	50	97

[a] These values (±2%) were determined by ^1H n.m.r. spectroscopy (200 MHz) of the monoesters in the presence of enantiomerically pure (*R*)-(+)-1-phenylethylamine.

References

1 For leading references, see G. M. Whitesides and C.-H. Wong, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 617; Ciba Foundation Symposium 111, Enzymes in Organic Synthesis, 1985; J. B. Jones, *Tetrahedron*, 1986, **42**, 3351.
2 A. B. Attygalle and E. D. Morgan, *Chem. Soc. Rev.*, 1984, **13**, 245; M. S. Blum, Am. Chem. Soc. Symp. No. 276, ed. P. A. Hedin, 1985, 393.
3 M. Kurihara, K. Kamiyama, S. Kobayashi, and M. Ohno, *Tetrahedron Lett.*, 1985, **26**, 5831.
4 G. Cignarella and G. Nathansson, *J. Org. Chem.*, 1961, **26**, 1500.
5 F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, and P. Szmulik, *Bioorg. Chem.*, 1986, **14**, 176; F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, and T. Norin, *Tetrahedron Lett.*, 1985, **26**, 4957.
6 L. K. P. Lam, R. A. H. F. Hui, and J. B. Jones, *J. Org. Chem.*, 1986, **51**, 2047; G. Guanti, L. Banfi, E. Narisano, R. Riva, and S. Thea, *Tetrahedron Lett.*, 1986, **27**, 4639.
7 F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, and T. Norin, *Appl. Microbiol. Biotechnol.*, 1985, **21**, 16.
8 D. H. R. Barton, Y. Hervé, P. Potier, and J. Thierry, *J. Chem. Soc., Chem. Commun.*, 1984, 1298.
9 L. Guoqiang, M. Hjalmarsson, H.-E. Högberg, K. Jernstedt, and T. Norin, *Acta Chem. Scand., Ser. B*, 1984, **38**, 795; M. Hjalmarsson and H.-E. Högberg, *ibid.*, 1985, **39**, 793.

‡ A typical batch contained 1 mmol substrate (**1**) dissolved in 75 ml of 0.25 M $(CH_2OH)_3CNH_2$–HCl (Tris–HCl), pH 7.5, 25% DMSO. Using 1.5 mg PLE (Sigma, batch no. 34F-8110) the hydrolysis was completed within 6 h at 30 °C.

§ Satisfactory spectroscopic data (^1H and ^{13}C n.m.r., mass spectra) were obtained for all new compounds.