Tetrahedron Letters, Vol.31, No.11, pp 1615-1616, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ENHANCED OPTICAL PURITY OF 3-HYDROXYESTERS OBTAINED BY BAKER'S YEAST REDUCTION OF 3-KETOESTERS

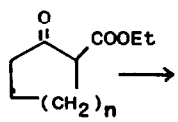
Vassilis Spiliotis, Demetris Papahatjis and Nikitas Ragoussis*.
Vioryl S.A. Research Department, Kato Kifissia, 145-64 Athens, GREECE.

Abstract : Fermenting Baker's yeast, enclosed in a dialysis tube, reduces efficiently 3-ketoesters added to the surrounding subtonic solution, to the corresponding 3-hydroxyesters in good yield (45-55%) and enhanced optical purity (ee 96-97%).

Reduction of 3-ketoesters by fermenting Baker's yeast is a synthetically significant procedure for the preparation of 3-hydroxyesters in good chemical yield and high optical purity[1,2]. As the optically active 3-hydroxyesters are valuable building units for the synthesis of various natural products[1], efforts have been made to ameliorate their enantiomeric excess.

In this paper we describe a very simple method of 3-ketoester reduction by fermenting Baker's yeast, according to which the fermenting medium is enclosed in a dialysis tube and the substrate is added to the surrounding subtonic solution. Thus we obtain 3-hydroxyesters of high enantiomeric excess, without any operational difficulty, even in relatively large scale experiments.

Typical experimental procedure : 60 g of Baker's yeast were dispersed in 100 ml of a 20% sucrose solution in tap water. The suspension was introduced in a 20 cm long dialysis tube (3.5 cm internal diameter) both ends of which were tightly attached to wide bore funnels and the tube was submerged in a stirred 10% sucrose solution (1 L). Once the fermentation was well set about, 0.1 mol of the 3-ketoester were added to the surrounding clear solution. Every twelve hours additional 50 ml of 20% sucrose solution were added through the funnels to the dialysis tube. At the end of the reaction the higher concentration of sucrose in the outside vessel caused a shrinking of the dialysis tube, which was removed, rinsed with water and discarded. The remaining clear solution was saturated with sodium chloride and easily extracted with diethylether. The obtained crude 3-hydroxyester was finally purified by careful distillation.

SUBSTRATE	PRODUCT	PRESENT WORK Yield %	$[a]^{25}_D$	ee %	LITERATURE Ref	$[a]^{25}_D$	ee %
$CH_3\overset{O}{\overset{\|}{C}}CH_2COOR$	$CH_3\overset{OH}{\overset{\|}{C}}HCH_2COOR$ R= Et	48	+41.1	96	1	+37.2	84-87
	R= Bu	50	+35.1	>97	4	+30.8	>90
	n=1	55	+14.5	>97	5	+14.1	--
	n=2	47	+27.9	>97	6	+24.2	86

The enantiomeric excess (ee %) has been determined by HPLC analysis of the MTPA esters obtained by esterification with (+)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride in pyridine solution[3] (MTPA Mosher's reagent). Instrument: Perkin Elmer Series 4. Column : Spherisorb ODS 5μ 25x4.6 mm. Solvent systems: Water/Acetonitrile 40/60 or water/methanol 32/68, 1 ml/min. Detection : UV detector λ = 210 nm.

The low concentration of the substrate in the fermenting medium[2], is a major factor contributing to the improved enantioselectivity of the Baker's yeast reduction of 3-ketoesters. Thus, we can reasonably assume that, use of a dialysis tube to separate the substrate and yeast improves the optical yield by limiting the local concentration of the substrate reaching the microorganism.

The main advantages of the described procedure are: a) The simplicity of the operation, b) The ease of the removal of the yeast's cells at the end of the reduction and the subsequent work up and c) The high optical purity of the products.

Acknowledgements : We thank the Greek General Secretary of Research and Technology for partial financial support (ΠΑΒΕ Β39 86).Thanks are also due to Dr V. Tychopoulos for carrying out the HPLC analysis.

REFERENCES AND NOTES

1. D. Seebach, M.A. Sutter, R.H. Weber and M.X. Zuger *Org. Synth.* 1985, 63, 1
2. B. Wipf, E. Kupfer, R. Bertazzi and H.G.W. Leuenberg *Helv. Chim. Acta* 1983, 66, 485.
3. J.A. Dale and H.S. Mosher *J. Am. Chem. Soc.* 1973, 95, 512.
4. D. Seebach and M.X. Zuger *Helv. Chim. Acta* 1982, 65, 495.
5. B.S. Deol, D.D. Ridley and G.W. Simpson *Aust. J. Chem.* 1979, 29, 2459.
6. G. Frater *Helv. Chim. Acta* 1980, 63, 1383.

(Received in UK 30 January 1990)