Tetrahedron Letters, Vol.30, No.2, pp 261-264, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSELECTIVE LIPASE-CATALYSED HYDROLYSIS OF ESTERS OF EPOXY SECONDARY ALCOHOLS: AN ALTERNATIVE TO SHARPLESS OXIDATION

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Summary The enantioselectivity and yield of lipase-catalysed hydrolyses of epoxy butanoates (4) depends on R. Sharpless oxidation of the secondary allylic alcohol (8,R^2=Pr) established that in the lipase-catalysed hydrolysis of (4,R^2=Pr) the threo-isomer gave higher ee than the erythro-isomer.

The enantioselective enzyme-catalysed hydrolysis[1] of esters (1) of 2,3-epoxy primary alcohols provides an alternative to the Sharpless oxidation[2] of allylic alcohols as a route to optically active 2,3-epoxy primary alcohols. However, the enzyme-catalysed hydrolysis of esters (2) of epoxy secondary alcohols as an alternative to the Sharpless oxidative kinetic resolution, leading to optically active allylic and epoxy secondary alcohols, does not seem to have been examined apart from a study[3] of the cyclic epoxy esters (3). We report here our preliminary investigations of the use of porcine-pancreatic lipase[4] for the hydrolysis of the epoxy butanoates (4,R^2=Et,Pr,$CH_2CH_2CO_2Et$). We were particularly interested in the epoxy diester (4,R^2=$CH_2CH_2CO_2Et$) as an intermediate and a model for the synthesis of optically active potential leukotriene antagonists [5,6,7] and were conscious of potential difficulties in the application of the Sharpless oxidation to the allylic alcohol ester (8,R^2=$CH_2CH_2CO_2Et$).[8]

The allylic alcohols (8,R^2=Et and R^2=Pr)[9] were prepared by reaction of cinnamaldehyde with EtMgBr and PrMgBr respectively. The ethoxycarbonyl allylic alcohol (8,R^2=$CH_2CH_2CO_2Et$)[10] was prepared by ZnI_2-catalysed reaction of cinnamaldehyde with 1-ethoxy-1-trimethylsilyloxy-cyclopropane.[11] Epoxidation of the allylic alcohols (8) with m-chloroperoxybenzoic acid followed by reaction with butanoic anhydride in pyridine afforded the epoxy butanoates (4).[10] Preparative layer chromatography (p.l.c.) of the epoxy butanoates (4) on silica gel allowed the separation of the racemic diastereoisomers and the hydrolyses (Table 1) were carried out on the more polar isomer for (4,R^2=Et and R^2=$CH_2CH_2CO_2Et$) whereas both diastereoisomers of (4,R^2=Pr) were investigated. The unreacted epoxy butanoates (4) and the epoxy alcohols (5) were separated by p.l.c. and the enantiomeric excesses of the epoxy alcohols (5) were determined from integration of the ^{19}F n.m.r. spectra of the diastereomeric mixture of the α-methoxy-α-trifluoromethylphenylacetates (MTPA esters) (6).[10,12]

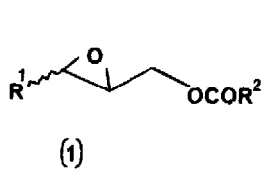
Catalytic Sharpless oxidation[2] of the racemic allylic alcohol (8,R^2=Pr) with L-(+)-di-isopropyltartrate/tert.-butyl hydroperoxide/$Ti(O\text{-}Pr^i)_4$ to 50% conversion, as monitored by g.l.c., afforded a mixture of the allylic alcohol (8,R^2=Pr) and the epoxy alcohol (5,R^2=Pr).[9] Acetylation of the mixture gave the acetates (7,R^2=Pr)[10] and (9,R^2=Pr)[10] which were separated

Table 1: Porcine Pancreatic Lipase-catalysed Hydrolysis

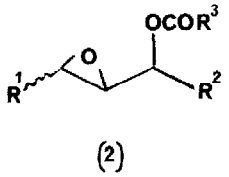
EXPERIMENT	Compound[a] 4 R^2=	Reaction[b] Time h	Ester Consumed %	Alcohol Yield Calc. on Ester Consumed %	Alcohol ee %(±5)
1	Et	5	49	50	100
2	Et	6	57	52	85
3	Pr	6	35	16	100
4	Pr	6	30	29	60
5	$CH_2CH_2CO_2Et$	6	48	22	56

a The experiments 1,2,4 and 5 were carried out on the more polar diastereoisomer. Experiment 3 employed the less polar diastereoisomer.

b Reactions were carried out at 23°C in a phosphate buffer at pH 8.6 and were terminated when the pH had fallen to a constant value (ca 7.9).



(1)



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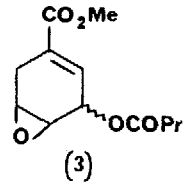
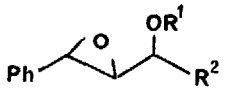
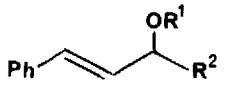
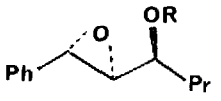


(3)





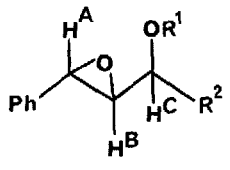


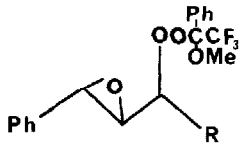
(4) R^1=COPr
(5) R^1=H
(6) R^1=PhC(OMe)(CF3)CO(R)
(7) R^1=Ac

(8) R^1=H
(9) R^1=Ac

(10) R=H
(11) R=PhC(OMe)(CF3)CO(R)

Table 2: Selected NMR Data

	^{1}H n.m.r. ($CDCl_3$ solutions)				
	δ ppm			J Hz	
R^1 R^2	H^A (d)	H^B (dd)	H^C (q)	AB	BC
R^1=COPr R^2=Et	3.77	3.10	4.83	2	6
R^1=COPr R^2=Pr(less polar)	3.88	2.97	4.90	2	6
R^1=COPr R^2=Pr(more polar)	3.77	3.08	4.90	2	6
R^1=COPr R^2=$CH_2CH_2CO_2Et$	3.71	3.07	4.87	2	6
R^1=H R^2=$CH_2CH_2CO_2Et$	3.93	3.07	3.93	2	4

	^{19}F n.m.r. (84.6 MHz) ($CDCl_3$ solutions)	
	ν Hz (downfield of 100% CF_3CO_2H external standard)	
	Diastereoisomers	
	1	2
R=Et	587	566
R=Pr (less polar)	591	567
R=Pr (more polar)	570	555
R=$CH_2CH_2CO_2Et$	595	574

by p.l.c. on silica gel. Hydrolysis of the epoxy acetate (7,R^2=Pr) with K_2CO_3/MeOH followed by esterification with MTPA-Cl[12] gave a single diastereoisomer (11)[10] which is presumed[2] to be derived from the erythro epoxy alcohol (10) which has the absolute configuration depicted. It was established from the ^{19}F n.m.r. spectrum that the MTPA ester (11) was identical with the minor component of the diastereomeric mixture (6,R^2=Pr) obtained from lipase-catalysed hydrolysis of the more polar epoxy butanoate (4,R^2=Pr).

As can be seen from Table 1, the enantioselectivity of the hydrolyses and conversions are structure dependent. The relatively low ee obtained for the epoxy butanoate (4,R^2=$CH_2CH_2CO_2Et$) which was of special interest, was disappointing. However, no attempt has been made to optimise conditions and improvements may be possible by variation of the enzyme system and/or the ester moiety employed. The interesting dependence of enantioselectivity on erythro versus threo stereochemistry (experiments 3 and 4) was similar to that observed in the study[3] of cyclic epoxy esters (3).

Acknowledgement We thank the University of Technology, Loughborough for a research studentship to M.R.-E.

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(Received in UK 14 November 1988)