

ENZYMATIC RESOLUTION OF RACEMIC BICYCLIC LACTONES BY HORSE LIVER ESTERASE

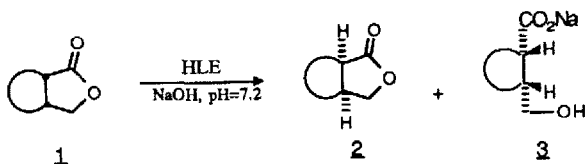
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Abstract : Optically active lactones were prepared by Horse Liver esterase catalyzed hydrolysis of bicyclic γ -butyrolactones.






Horse Liver esterase (HLE) is less employed in organic synthesis than Porcine Liver esterase (PLE). Nevertheless its enantioselectivity in enzyme-catalyzed hydrolysis appears complementary. For example the resolution of δ -substituted δ -valerolactones and ϵ -substituted ϵ -caprolactones was achieved using this enzyme (1).

In this letter are reported our results concerning the resolution of cis-fused bicyclic γ -butyrolactones 1 using HLE. Lactones 1 were prepared by NaBH_4 reduction of the corresponding anhydrides (2). The hydrolyses were carried out with crude HLE (Horse Liver acetone powder from Sigma) and after 55% conversion the remaining lactones 2 were extracted with ether. Acidification of the aqueous phase containing the hydroxycarboxylates 3 gave the antipodal lactones 4 of 2. We did not try to improve the ee's of lactones 4, however as usual it should be done in reactions stopped after 45% conversion. Our results are reported in the table. The optically active lactones 2 here prepared in two (1b, 1d, 1e) or three steps (1a, 1c) from commercial meso-anhydride and meso-diacid, have been previously obtained in five steps using enzymatic resolution of meso-diester (3) or meso-diols (4). Our new method allows the preparation of the two antipodal lactones one being inaccessible by the previously described enzymatic hydrolysis or oxydation methods (3,4,7).



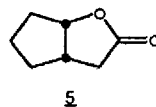
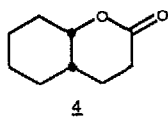
The HLE catalyzed hydrolysis of lactones 1a - 1e occurred mainly by reaction of the enantiomer with 1S absolute configuration. Excellent enantiomeric excesses (ee) were obtained in the hydrolysis of small carbocyclic ring lactones 1a, 1b. In the case of the cyclopentanic lactone 1c a very low ee was observed (5). The moderate ee obtained with the cyclohexanic lactone 1d is probably due to the boat conformation (6) of the cyclohexane ring which should disfavor the enzymatic recognition. We have observed a dramatic effect of bovine serum albumine in the case of the cyclohexenic lactone 1e and no effect with the lactones 1a-1d. While for the cyclopropanic and cyclobutanic lactones 1a, 1b the hydrolyses were conducted in a buffer solution, for the other lactones it was necessary to use calcium chloride (see (1)). Hydrolysis of lactones 1 with enzymes such as Pig Liver esterase or Porcine Pancreatic lipase gave lactones 2 with much lower ee : for example with the lactone 1d we isolated after 55% conversion the lactone 2d with 40% ee (PLE hydrolysis) or 0% ee (PPL hydrolysis).

The configurations and the ee's of the lactones 2 were determined by comparison of their optical rotations with those reported (3d,7). These ee's were confirmed by examining the ¹H NMR behavior of the diols, derived from these lactones by addition of methyl lithium, in the presence of $\text{Eu}(\text{tfc})_3$ (see (1)).

LACTONE	Method ^(a)	Time for 55% conversion	LACTONE 2				LACTONE 4			$(\alpha)_D^{25}$ lit. ⁽⁷⁾ (CHCl ₃)
			Yield (%)	$(\alpha)_D^{25}$ (THF) ^b	ee%	Contig.	Yield (%)	$(\alpha)_D^{25}$ (THF) ^b	ee%	
 1a	A	3.5 h	41	+61°	98	1R, 5S	50	-47°	76	+61.8°
 1b	A	3 h	42	-95°	80	1R, 5S	48	+71°	60	-118.7°
 1c	B	15 h	43	-3°	3	1R, 5S	47	-	-	-96.9°
 1d	B	13 h	40	-23°	47	1R, 6S	50	+18°	38	-48.8°
 1e	B	7 h	33.5	+30°	44	1R, 6S	50	-24°	36	+67.1°
	C	7 h	34	+64°	95	1R, 6S	50	-52°	77	

a) Method : Reactions were performed using 0.6 g of lactone 1 in 15 ml of solution (In brackets are indicated ratio of lactone, HLE and Bovine Serum Albumine weights) : A (1/0.5/0) in the H₂O, Na₂HPO₄ (0.1M) ; B (1/1/0) in H₂O, CaCl₂ (0.9M) ; C (1/1/1) in H₂O. The pH was maintained at 7.2 by addition of 2M NaOH solution. Example of reaction : from 603 mg of lactone 1a was isolated after a 12 hours continuous extraction with ether 247 mg (Y = 41%) of lactone 2a ($(\alpha)_D^{25} = +60.8^\circ$). The aqueous phase was acidified (pH: 2, 3 hours) and a 12 hours continuous extraction with ether have delivered 304 mg (Y = 50%) of lactone 4a ; b) c = 2.

Structurally different bicyclic lactones give similar results. For instance HLE hydrolysis of lactone 4 in the presence of calcium chloride gave an optically active lactone with 60% ee (8) after 55% conversion (8) and no resolution was observed with the lactone 5 using HLE, PLE or PPL.



References

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- 2) D.M. Bailey, R.E. Johnson, J. Org. Chem., 35, 3574 (1970). Cis-cyclopropane-1,2 dioic acid anhydride and cis-cyclopentane-1,2 dioic acid anhydride were obtained by pyrolysis of the corresponding cis-trans-1,2-dioic acids (300°C, 12 h for the cyclopropane and 210°C, 20 h for the cyclopentane). We thank Mrs J. Marguerite who prepared some starting materials.
- 3) a) P. Mohr, N. Waespe-Sarcevic, C. Tamm, K. Gawronska, J.K. Gawronski, Helv. Chim. Acta, 66, 2501 (1983) ; b) M. Schneider, N. Engel, P. Hönicke, G. Heinemann, H. Görisch, Angew. Chem. Int. Ed., 23, 67 (1984) ; c) H.J. Gais, K.L. Lukas, Angew. Chem. Int. Ed., 23, 142 (1984) ; d) G. Sabbioni, J.B. Jones, J. Org. Chem., 52, 4565 (1987).
- 4) K. Laumen, M. Schneider, Tetrahedron Lett., 26, 2073 (1985) ; W. Kasel, P.G. Hultin, J.B. Jones, J.C.S. Chem. Commun., 1563 (1985).
- 5) The conformational mobility of the cyclopentanic ring should disfavor the enzymatic recognition. See also (3d).
- 6) The boat conformation was deduced from the NMR spectra and was confirmed by molecular calculations (MM2).
- 7) I.J. Jakovac, H.B. Goodbrand, K.P. Lok, J.B. Jones, J. Amer. Chem. Soc., 104, 4659 (1982).
- 8) The absolute configuration of this lactone has not been yet determined. $[\alpha]_D^{25}$ measured = -28 (c = 2, THF).

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