Enantiomerically Selective Pig Liver Esterase-catalysed Hydrolyses of Racemic Allenic Esters

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Pig liver esterase-catalysed hydrolyses of variously substituted racemic allenic esters proceed with predictable enantiomeric selectivity, with the highest (93%) enantiomeric excess values being observed for the most highly substituted substrates.

Interest in allenes as synthetic intermediates and targets continues to grow,[1—7] with many of the naturally occurring allenes being chiral.[4—7] So far, methods for resolving allenic racemates have been based almost exclusively on classical, and often laborious, resolution methodology.[7,8] Despite the well documented exploitation of the abilities of enzymes to discriminate between enantiomers in preparative-scale resolutions of racemates,[9] the number of examples of stereospecific enzyme-catalysed transformations of allenic substrates is small.[10] In the past, the fact that many allenes inactivate enzymes, often by acting as suicide inhibitors,[5,6,11] may have acted as a deterrent to enzymic resolution investigations. However, using appropriate enzymes and substrates, this difficulty can be avoided, and enzyme-mediated resolution of allenes can become a generally useful procedure. This is now demonstrated by pig liver esterase (PLE, EC 3.1.1.1)-catalysed hydrolyses of the racemic allenic esters (±)-(**1a**—**m**), which proceed with considerable enantiomeric selectivity, particularly when the allenic substrates are highly substituted.

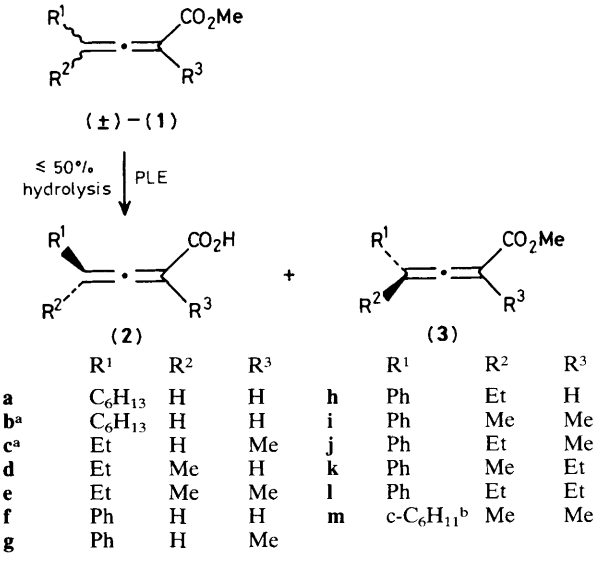
The racemic ester substrates (±)-(**1a**—**m**)† were prepared by literature methods,[12—14] or minor modifications thereof. Preparative-scale (up to 2 mmol of substrate) PLE-catalysed hydrolyses of (±)-(**1a**—**m**) to (**2, 3a**—**m**) (Scheme 1) were performed at pH 7. The reactions were carried out on a 1—1.5 mmol scale, and were worked up by extracting with ether, first at pH 7 to recover the unchanged ester, and then at pH 2 to isolate the acid product. Further purification was by chromatography on Sephadex LH-20 with chloroform–hexane elution. The results are summarised in Table 1. The reactions were terminated at, or close to, the 50%-of-hydrolysis point, except for (±)-(**1a**, **f**, **g**), for which the reduced yields are attributable to slow substrate- or product-inhibition leading to partial inactivation of PLE during the hydrolyses. Generally, the more highly substituted the allene, the slower the rate of PLE-catalysed hydrolysis. Also, ethyl esters are hydrolysed more slowly than methyl esters. Most of the enantiomeric

† All substrates and products were fully characterised.

Table 1. PLE-catalysed hydrolyses[a] of allenic esters (±)-(**1a—m**).

Substrate	Reaction time	% Hydrolysis	Acid product [% Yield, Abs. config.,[b] % e.e.[c]]	Recovered ester [% Yield, Abs. config.,[b] % e.e.[c]]
(**1a**)	1 day	31	(**2a**) [28, *S*(+), 38[15](45[d])]	(**3a**) [54, *R*(−), (9[d])]
(**1b**)	4 days	38	(**2b**) [20, *S*(+), 22[15](26[d])]	(**3b**) [44, *R*(−), (6[d])]
(**1c**)	13 h	50	(**2c**) [47, *S*(+), 7[13](6[d])]	(**3c**) [53, *R*(−), (5[d])]
(**1d**)	1.5 h	50	(**2d**) [47, *S*(+), 6[16](10[d])]	(**3d**) [31, *R*(−), 8[16](10[d])]
(**1e**)	22 h	50	(**2e**) [42, *S*(+), 21[e](22[d])]	(**3e**) [36, *R*(−), 23[e](23[d])]
(**1f**)	6 h	18	(**2f**) [17, (±)]	(**3f**) [71, (±)]
(**1g**)	6 h	10	(**2g**) [7, *R*(−), 16[13](16[d])]	(**3g**) [81, *S*(+), (1[d])]
(**1h**)	22 h	50	(**2h**) [46, *R*(−), 31[13](34[d])]	(**3h**) [50, *S*(+), (38[d])]
(**1i**)	29 h	50	(**2i**) [33, *R*(−), 90[13](90[d])]	(**3i**) [50, *S*(+), (61[d])]
(**1j**)	4 days	44	(**2j**) [33, *R*(−), 88[13](88[d])]	(**3j**) [64, *S*(+), 36[13](39[d])]
(**1k**)	3 days[f]	54	(**2k**) [52, *R*(−), 63[13](78[d])]	(**3k**) [43, *S*(+), 73[13](83[d])]
(**1l**)	2 days[f]	35	(**2l**) [17, *R*(−), 93[13](100[d])]	(**3l**) [79, *S*(+), 22[13](22[d])]
(**1m**)	3 days	51	(**2m**) [42, *R*(−), 32[e]]	(**3m**) [42, *S*(+), 31[e]]

[a] At 25 °C, pH 7. [b] Assigned by the method described in ref. 3, pp. 587—590, when correlations with literature rotations of known compounds were not possible. [c] Calculated on the basis of literature rotations unless designated otherwise. [d] By calculation.[3,17] All calculated e.e.s are shown in parentheses. [e] By n.m.r.[12] Attempted n.m.r. determinations of e.e.s were unsuccessful for all other allenes in this Table. [f] At 35 °C, pH 7.



	R[1]	R[2]	R[3]		R[1]	R[2]	R[3]
a	C_6H_{13}	H	H	**h**	Ph	Et	H
b[a]	C_6H_{13}	H	H	**i**	Ph	Me	Me
c[a]	Et	H	Me	**j**	Ph	Et	Me
d	Et	Me	H	**k**	Ph	Me	Et
e	Et	Me	Me	**l**	Ph	Et	Et
f	Ph	H	H	**m**	c-C_6H_{11}[b]	Me	Me
g	Ph	H	Me				

[a] Et ester. [b] Cyclohexyl.

Scheme 1

excess (e.e.) values shown in Table 1 are based on optical rotation or ^{1}H n.m.r. measurements. Where these direct correlations with literature standards were not possible, the e.e.s were based on calculated rotations[3] for the structure involved. The validity of the calculated values is confirmed by the excellent agreements between the observed and calculated e.e.s of Table 1, where both are available.

The enantiomeric selectivity of the hydrolyses is consistently (*S*)-ester selective when the C-4 substituents are relatively small or acyclic, as for (±)-(**1a—e**), and (*R*)-ester selective when the C-4 substitutents are relatively large or cyclic, as for (±)-(**1f—m**). This is as predicted by our two-binding-site active-site model.[18] The e.e. values of the acid (**2a—m**) and ester (**3a—m**) products are highest when the degrees of substitution at the C-2 and C-4 positions are greatest, with the enantiomeric purities of (**2i, j, l**) already being close to asymmetric synthetically acceptable levels. None of the Table 1 reactions has been optimised, and the e.e. levels will all be improved considerably when the hydrolyses are optimised using a technique for manipulating reaction conditions that has proved successful for other stereoselective PLE-mediated transformations.[18] We are currently carrying out e.e. optimisation, and also delineating further the generality of applying enzymes to the production of chiral allene stereoisomers.

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

Received, 16th June 1986; Com. 827

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