# Enzymatic Resolution of Chiral *N*-Alkyloxaziridine-3,3-dicarboxylic Esters

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Porcine pancreatic lipase provided enantioselective hydrolyses of chiral *N*-alkyloxaziridine-3,3-dicarboxylic esters.

The development of highly stereospecific and stereoselective methods of syntheses[1] of optically active compounds is one of the main goals of organic chemistry. In this respect, utilization of enzymes as catalysts in organic reactions has recently been the object of great attention.[2] It is well known[2] that enzymes are extremely versatile. They catalyse a broad spectrum of reactions and can simultaneously display high chemical, regiochemical and stereochemical selectivity in very mild experimental conditions.

In this paper we report the resolution of chiral *N*-alkyloxaziridine-3,3-dicarboxylic esters (**1a—d**) through the enzyme-catalysed hydrolysis of the racemic diesters. This is a new and more convenient method for obtaining optically active oxaziridines (**1**) with high optical purity. Oxaziridines of type (**1**) are characterized by molecular asymmetry due solely to the ring nitrogen atom and possess reactive ester groups on the ring carbon atom. They have previously been obtained in optically active form by asymmetric oxidation of the corresponding prochiral imines (**2**)[3] or by optical resolution of the racemic forms (**1**) carried out by the classical fractional crystallization of the diastereoisomeric salts of the monoacids (**3**) with chiral amines.[4]

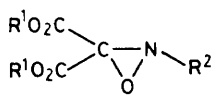
It has been recently reported[5,6] that lipases catalyse the enantioselective hydrolysis of a broad structural range of racemic esters.

We tested the hydrolytic ability of porcine pancreatic lipase (PPL) and lipase from *Candida cylindracea* on oxaziridines (**1a—d**). The enzymes were purchased from Sigma and were used without purification. Racemic oxaziridines (**1a—d**) were synthesized as described elsewhere.[7]

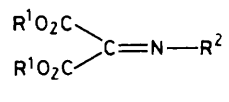
**Table 1.** Chiral oxaziridines (**1a—d**) from PPL hydrolysis.

| | Reaction conditions[a] | | Unchanged ester | | |
|---|---|---|---|---|---|
| Substrate | *t*/h | % conversion[b] | $[\alpha]_D$ | E.e.%[c] | Conf.[d] |
| (**1a**) | 3 | 70 | +66.8 | 87 | *R* |
| (**1b**) | 2 | 55 | +35.8 | 58 | *R* |
| (**1c**) | 10 | 50 | +35.8 | 45 | *R* |
| (**1d**) | 6 | 70 | +21.0 | 53 | *R* |

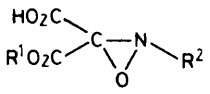
[a] All hydrolyses were performed in phosphate buffer (pH 7.5; 0.1 M) at room temperature. Reaction mixture composed of oxaziridine/lipase 1/1 (w/w). [b] Based on the monoacid (**3a—d**) recovered after enzymatic hydrolysis. [c] Optical yields (e.e. %) determined from n.m.r. spectra recorded in $CDCl_3$ solution and in the presence of a 5-fold excess of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol and by comparison of the optical rotations given in ref. 3, 4. [d] Assigned by n.m.r.-chiral-solvating-agent (c.s.a.) method[3] and by chiroptical behaviour of the optically pure compounds.[4]



(1)



(2)



(3)

**a**; $R^1$ = Me, $R^2$ = Bu$^t$
**b**; $R^1$ = Me, $R^2$ = Pr$^i$
**c**; $R^1$ = Et, $R^2$ = Bu$^t$
**d**; $R^1$ = Et, $R^2$ = Pr$^i$

It is interesting that while lipase from *C. cylindracea* hydrolyses the substrates (**1a—d**) without enantioselectivity, porcine pancreatic lipase (PPL) catalyses the stereospecific† and enantioselective hydrolysis of the diesters (**1a—d**).

The hydrolysis of racemic *N*-t-butyl-3,3-bismethoxycarbonyl oxaziridine (**1a**) with PPL in phosphate buffer (0.1 M; pH 7.5), up to 70% conversion (3 h), provided the unhydrolysed ester (**1a**) {20% yield; $[\alpha]_D$ +66.8°, *c* 3.232, $CHCl_3$; 87% enantiomeric excess (e.e.)[4]}. From the aqueous phase, after acidification,[4] we recovered the monomethyl ester (**3a**) (62% yield; $[\alpha]_D$ −20.8°, *c* 1.238, $CHCl_3$). The esterification of (**3a**) by diazomethane gave the oxaziridine diester (**1a**) ($[\alpha]_D$ −26.7°, *c* 2.431, $CHCl_3$; 36% e.e.).

To improve the optical purity of this (−) enantiomer (36% e.e.), a second PPL hydrolysis was performed for a short time (1 h); we obtained the monomethyl ester (**3a**) (30% yield; $[\alpha]_D$ −47.8°, *c* 0.772, $CHCl_3$) that, after conversion into the corresponding diester (**1a**) shows $[\alpha]_D$ −59.4° (*c* 1.459, $CHCl_3$; 80% e.e.). However, the same procedure applied to compounds (**1b—d**) provided oxaziridines with lower optical yields (45—60%) (see Table 1).

When applicable, this enzymatic method provides a simple, quick and cheap experimental procedure for obtaining chiral oxaziridines. The chemical yields of one enantiomer can be improved by the thermal racemization[7] of the unwanted form.

Moreover, to the best of our knowledge this is the first example of enzymatic resolution of compounds whose chirality is due solely to a pyramidal nitrogen atom.

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† The enzymatic hydrolysis affords the *N*-alkyloxaziridine-3,3-dicarboxylic acid monomethyl (or ethyl) ester in the single diastereoisomeric form obtained also from the chemical process (as indicated by $^1$H n.m.r. spectroscopy).

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