Tetrahedron: Asymmetry Vol. 1, No. 1, pp. 5-8, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Optically Active N-Chloro-2,2-bismethoxycarbonylaziridine by Enzymatic Hydrolysis.

Maria Bucciarelli, Arrigo Forni, Irene Moretti* and Fabio Prati

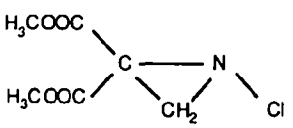
Dipartimento di Chimica dell'Università, via Campi, 183, 41100, Modena, Italy.

(*Received* 13 *November* 1989)

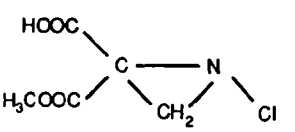
Abstract: N-Chloro-2,2-bismethoxycarbonylaziridine has been obtained with high enantiomeric purity by enzymatic hydrolysis; the first-order rate constant and the activation parameters for pyramidal inversion were determined.

It is well known[1] that ester hydrolases, such as esterases, proteases and lipases, catalyze the enantioselective hydrolysis of a broad structural range of racemic esters. Their employment has become of increasing importance for the synthesis of optically active compounds.

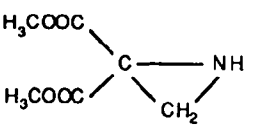
Recently, we found that lipases can be successfully used to resolve compounds such as N-alkyl-3,3-bismethoxycarbonyloxaziridines[2] whose chirality is due solely to a trivalent nitrogen atom. In this work we extended the use of lipases to the synthesis of chiral N-Chloro-2,2-bismethoxycarbonylaziridine (**1**). This compound is characterized by the presence of a highly electronegative substituent on the ring-nitrogen atom and ester groups on the ring-carbon atom and the availability of its optically pure form could be of interest to organic chemists.[3]



(**1**)



(**2**)



(**3**)

Hitherto, the approach to optically active N-chloroaziridines has required optically active starting materials[4] or the asymmetric chlorination of NH-aziridines.[5] The latter method, in particular, applied to the synthesis of the optically active compound (**1**), has failed.[5]

The results, reported here, show that the enantioselective enzymatic hydrolysis of racemic N-chloro-2,2-bismethoxycarbonylaziridine (**1**) has afforded, for the first time, compound (**1**) in nearly optically pure form. This method provides an easy and convenient route to optically active N-chloro-2,2-bismethoxycarbonylaziridine (**1**) in good chemical and optical yield.

Several hydrolases were tested (Table 1). Of these, α-Chymotrypsin and lipases from porcine pancreas, *Candida cylindracea* and *Rhizopus delemar* were quite active and catalyzed the stereospecific[6] and enantioselective hydrolysis of the diester (**1**). Enzymes such as pig liver esterase and lipases from *Aspergillus niger* and *Pseudomonas fluorescens* display catalytic activity but very low enantioselectivity.

Table 1. Enzymatic hydrolysis of (±)-(**1**) in the presence of ester hydrolases.

Hydrolases	Reaction conditions[a]		unreacted ester[b]		
	t/ h	conversion%[c]	yield (%)	$[\alpha]_D$[d]	e.e.%[e]
α-chymotrypsin	5	55	30	+51,6[f]	50
Lipase from *Rhizopus delemar*	4	70	27	-78,5	76
Lipase from *Candida cylindracea*	6	35	49	-35,2	34
Lipase from porcine pancreas	5	75	20	+16,3	16
Pig liver esterase	0,5	55	40	+1,1	-
Lipase from *Pseudomonas fluorescens*	25	35	55	+1,6	-
Lipase from *Aspergillus niger*	24	35	58	-1,5	-

[a] All hydrolyses were performed in phosphate buffer (pH 7.5; 0.1 M) at room temperature. The reaction mixture consisted of aziridine/enzyme 2/1 (w/w). [b] The physical and n.m.r. properties of (**1**) are consistent with those reported in ref. 5. [c] Based on the monoacid (**2**) recovered after enzymatic hydrolysis. [d] Data for chloroform solution. Fractional crystallization of partially optically active (**1**) afforded a sample $[\alpha]_D$ +105 (e.e. > 95%). [e] ±2%; optical yields (e.e.%) were 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. [f] The first- order rate constant (k 5.2 10^{-4} s^{-1}) and the activation parameters for pyramidal inversion ($\Delta G^{\neq}$ 24.6 Kcal/mol; $\Delta H^{\neq}$ 24.2 Kcal/mol; $\Delta S^{\neq}$ - 1.2 e.u.) were determined from thermal racemization in CCl_4 and in the 40 -60 °C temperature range.

Racemic N-chloroaziridine (**1**) was synthesized from the corresponding NH-aziridine[5] (**3**) by chlorination with t-butylhypochlorite, as described elsewhere.[7]

In a typical experiment, the commercially available enzyme (0.5g), purchased from Fluka or Sigma and used without purification, was added to a suspension of racemic N-chloro derivative (**1**) (1g) in phosphate buffer (50 cc. 0.1 M and NaCl 0.1 M; pH 7.5) at room temperature. The suspension was vigorously shaken and the reaction was stopped when 50 - 70% of conversion was reached.

The optically active unreacted diester (**1**) was isolated from the aqueous phase by simple extraction with CH_2Cl_2 followed by column chromatography on silica gel (petroleum ether/ethyl ether as eluant). The enantiomeric excesses (e.e.'s) were determined by ^1H n.m.r. spectroscopy using (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol as chiral solvating agent.

The quite high optical activity of (**1**) allowed us to determine the barrier to pyramidal nitrogen inversion ($\Delta G^{\neq}$ 24.6 Kcal/mol) by thermal racemization. The optical decay of a sample having $[\alpha]_D$ +51.6 was followed, in CCl_4 solution and in the 40-60 °C temperature range, by polarimetric determination. ^1H n.m.r. and t.l.c. showed no decomposition of the product during the process. The half-life for racemization of (+)-(**1**) was 32 h. at 20 °C.

This peculiarity made every manipulation critical; nevertheless, fractional crystallization of the partially optically active compound (**1**) from ethyl ether improved its enantiomeric purity to 95% (as evaluated by ^1H n.m.r. spectroscopy).

The enzymatic hydrolysis product (**2**) was recovered from the aqueous phase in good chemical yield by evaporation of the water *in vacuo* at room temperature followed by treatment with an ion-exchange resin in ethyl ether at 0°C. The generally low enantiomeric excess of (**2**), (e.e. < 30%) was estimated through its conversion to the corresponding diester (**1**) by esterification with diazomethane.

These results further demonstrate the great efficacy of hydrolases in enantiomer differentiation and, in our opinion, indicate that enzymatic transformation represents an easy and useful route to the preparation of several three-membered heterocycles containing a chiral nitrogen atom with high enantiomeric purity and in synthetically useful quantities.

Acknowledgment

M.B., A.F., I.M., F.P. thank the C.N.R. Rome, for financial support.

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