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An efficient enzymatic method for the separation of stereoisomeric *cis* and *trans*-glycidic esters synthesised via Darzen's condensation reactions

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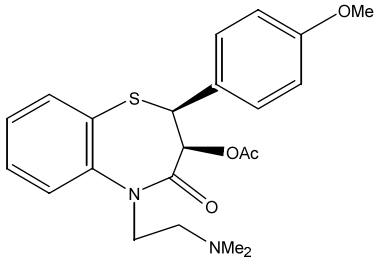
Abstract—Pig's liver esterase (PLE) was used efficiently in phosphate buffer for the separation of stereoisomeric mixtures of *cis*/*trans*-ethyl arylglycidates, produced via Darzen's condensation reactions.

Epoxides are widely distributed in nature and are of industrial, mechanistic and biochemical interest.[1] Squalene 2,3-oxide is the biogenetic precursor of sterols. Leukotriene A (LTA) is the biogenetic precursor of the leukotrienes LTC, LTD and LTE which are important natural mediators of allergic asthma.[2] The ease of preparation of epoxides and their facile ring opening have made them versatile intermediates in organic synthesis.[3]

One of the well established methods in epoxide synthesis is Darzen's methodology.[4] Synthesis of glycidic esters by this protocol does in fact yield both geometrical isomers and evidence for their occurrence is found in the literature.[5] On the other hand the need for either isomers in pure form is a prime objective in the synthesis of pharmaceutically important products. For example, the synthesis of (2*S*,3*S*)-diltiazem **1**, an enantiomerically pure drug possessing calcium antagonist activity[6] and used as a coronary vasodilator, involves methyl *trans*-*p*-methoxyphenylglycidate as the first intermediate.[7] In a practical chemoenzymatic synthesis of the Taxol C-13 side-chain, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine **2**, *trans*-β-phenylglycidic esters were used as starting materials.[8]

As part of our continuing program in the synthesis of chiral synthons which can be exploited in the synthesis of biologically important substrates,[9] herein we report a mild and efficient enzymatic method for the separation of *cis* and *trans*-stereoisomers produced via Darzen's condensation reactions.

Substrates **3a**–**g** were prepared by Darzen's methodology using the corresponding aromatic aldehydes and ethyl chloroacetate in the presence of KO^{t}Bu.[10] The reaction furnished both *cis* and *trans* isomers, with the latter predominating (Table 1). The structures of the products were established by spectroscopic analysis and the ratio of the *cis*/*trans* isomers was measured directly from ^{1}H NMR (500 MHz) on the basis of the α-hydrogen in the glycidates. Separation of the geometric isomers produced in this study was not possible by conventional methods (fractional distillation or chromatography). Therefore, we examined an enzymatic method using pig's liver esterase (PLE) as catalyst. This enzyme has been utilised in asymmetric synthesis,[11] separation of stereoisomers[12] and for the hydrolysis of ester functions contained in hydrolytically sensitive compounds.[13]



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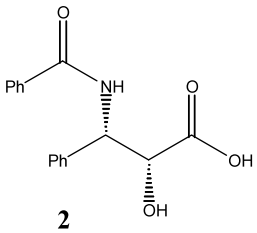

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Keywords: epoxides; Darzen's reaction; glycidic esters; enzyme; PLE.

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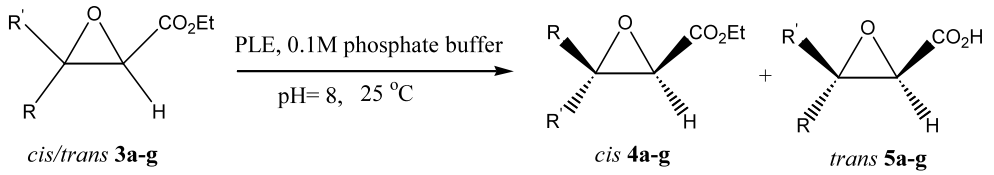

cis/trans **3a-g** *cis* **4a-g** *trans* **5a-g**

Scheme 1.

Table 1. Separation of *cis*/*trans*-glycidates from the Darzen's reaction using PLE

Entry	R	R′	*cis*/*trans* Ratio	Reaction time (h)	Conversion (%)	**4a**–**g** yield (%)[a]	**5a**–**g** yield (%)[a]
3a	C_6H_5	H	43/57	7.5	57	38	51
3b	C_6H_5	Me	39/61	9	61	36	57
3c	*p*-Me-C_6H_4	H	35/65	8.5	65	32	61
3d	*p*-Me-C_6H_4	Me	40/60	9.5	60	39	56
3e	*p*-MeO-C_6H_4	H	32/68	8	68	27	61
3f	*m*-NO_2-C_6H_4	H	30/70	10	70	27	67
3g	*p*-NO_2-C_6H_4	C_6H_5	45/55	13.5	55	40	49

[a] Isolated yields.

Substrates **3a**–**g** were incubated with PLE (55 μl/mmol) in 0.1 M phosphate buffer (pH 8) at room temperature. The reaction was stopped at the desired conversions (Table 1). Under these conditions the *trans* isomer was hydrolysed to the related glycidic acid (**5a**–**g**) leaving the *cis* isomer (**4a**–**g**) intact in a completely stereoselective reaction (Scheme 1). In order to evaluate the unique stereoselectivity observed in this study, substrates **3a**–**b**, after reaching the desired level of conversion (Table 1), were exposed to PLE hydrolysis for a longer reaction time; however, no trace of *cis* isomer hydrolysis was observed. To confirm the purely enzymatic nature of this separation reaction, a control reaction was conducted on substrate **3a** in the absence of the enzyme. After 7.5 h, the usual work up of the reaction afforded starting materials with no trace of the hydrolysis products.

In conclusion, we have developed an easy and quantitative method for the separation of arylglycidates produced in the Darzen's reaction.

General procedure:

The ethyl glycidates (**3a**–**g**) were suspended in a 0.1 M phosphate buffer solution (10 ml/mmol) at pH 8 and incubated with PLE (55 μl/mmol, EC 3.1.1.1 purchased from Sigma as a suspension in 3.2 M $(NH_4)_2SO_4$ solution) at 25°C. The pH was maintained by continuous addition of 0.25 M aqueous NaOH solution using a burette. After reaching an appropriate reaction conversion (Table 1), the reaction was stopped by adding aqueous sodium carbonate until pH 10. The aqueous reaction mixture was extracted with ether and the combined ether extracts were dried ($MgSO_4$) and evaporated to give the unreacted *cis*-glycidates (**4a**–**g**).

The remaining aqueous layer was acidified with dilute H_2SO_4, to pH 4 and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give the *trans*-glycidic acids (**5a**–**g**).

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