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Synthesis of planar-chiral [2.2]paracyclophanes by biotransformations: screening for hydrolase activity for the kinetic resolution of 4-acetoxy-[2.2]paracyclophane

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Abstract

The synthesis of enantiomerically pure 4-hydroxy-[2.2]paracyclophane using enzyme catalysed transesterification, esterification and hydrolysis reactions was investigated. While transesterification and esterification reactions completely failed, 19 of 28 enzymes were found to hydrolyse 4-acetoxy-[2.2]paracyclophane **1** to the desired product. Whereas most of the enzymes showed low to moderate enantioselectivity, with *Candida rugosa* lipase (CRL) an enantiomeric excess of 99.5% was obtained after 65% conversion corresponding to an enantiomeric ratio *E* of 20. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Enantiomerically pure planar chiral [2.2]paracyclophanes have interesting properties and seem to be useful auxiliaries in different applications. As shown recently by Issberner et al. [1], dendrimers bearing terminal planar chiral [2.2]paracyclophanes can be employed for complexation of a couple of metal cations and are therefore foreseen as asymmetric homogenous catalysts.

On the other hand, enantiomerically pure [2.2]paracyclophanes have been used as chiral auxiliaries in the transition metal catalysed asymmetric synthesis of β-hydroxy-α-amino acids [1,2].

Former attempts in the preparation of enantiomerically pure [2.2]paracyclophanes included diastereomeric resolution [2,3] and chiral HPLC [4], but the yields were generally too low to be useful in preparative terms.

In a previous paper we have reported on a preparative useful method for the synthesis of 4-formyl-[2.2]paracyclophane [5]. Asymmetric reduction of the substrate was carried out using whole cells of *Saccharomyces cerevisiae* as a biocatalyst.

For planar chiral ferrocenes [6,7] and [2.2]paracyclophanes [8], enantioselective hydrolysis of esters and esterification of alcohols

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using lipases and esterases have been reported, but in the latter case only low enantiomeric excess could be obtained.

Our present contribution deals with the screening for biocatalysts useful for the preparation of enantiomerically pure 4-hydroxy-[2.2]paracyclophane. Several commercially available lipases and esterases have been applied in hydrolysis, esterification and transesterification reactions.

2. Experimental

2.1. Chemicals and enzymes

Unless otherwise stated, all chemicals used were of reagent grade and purchased from Fluka Chemie (Buchs, Switzerland). 4-Hydroxy-[2.2]-and-4-acetoxy-[2.2]paracyclophane were synthesised according to Hopf et al. [9] and Ohse and Hopf [B. Ohse, H. Hopf, unpublished results]. Lipases and esterases listed in Table 1 were either purchased or gifts from Amano Pharmaceutical (Nagoya, Japan), Asahi Chemical Industry (Tokyo, Japan), Biocatalysts (Pontybridd, UK), Boehringer Mannheim (Penzberg, Germany), Showa Denko (Tokyo, Japan), Fluka (Neu-Ulm, Germany), Gist-Brocades (Delft, The Netherlands), Novo (Bagsvaerd, Denmark), and Solvay Enzymes (Hannover, Germany), respectively.

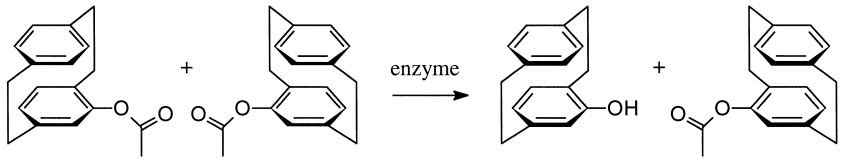
2.2. Screening for stereoselective hydrolysis of 4-acetoxy-[2.2]paracyclophane RS-**1**

Enzymes were screened using a biphasic system because of the poor solubility of the substrate. About 100 mg of the enzyme preparation were solved in 1.8 ml 0.1 M potassium–phosphate buffer, pH 7.0. The reaction was started by adding 1.2 ml solution of 4.3 mM *RS*-**1** in toluene. The reaction mixture was stirred at

Table 1
Screening for hydrolyases stereoselective for the hydrolysis of 4-acetoxy-[2.2]paracyclophane **1**. The enantiomeric ratio *E* was calculated using the model of Chen et al. [10]

Enzyme	Source	Supplier	Enantiomeric ratio E
Lipase AY	*Candida rugosa*	Amano	20.0
Lipase	*C. rugosa*	Fluka	17.0
Lipase	*C. antarctica* fraction A	Boehringer Mannheim	5.2
Lipase A	*Aspergillus niger*	Amano	4.0
Lipase	*Rhizopus*	Solvay-Enzymes	4.0
Lipase	*Humicola lanuginosa*	Biocatalysts	3.0
Lipase	*Mucor miehei*	Biocatalysts	3.0
Alcaline Lipase	*Stiowa*	Showa Denko	3.0
Lipase R	*Penicillium roquefortii*	Amano	2.0
Lipase	*C. rugosa*	Boehringer Mannheim	1.8
Lipase D	*Rhizopus delemar*	Amano	1.5
Lipase F	*R. javanicus*	Amano	1.5
Lipase	*Pseudomonas alcaligenes*	Gist-Brocades	1.5
Lipase M	*M. javanicus*	Amano	1.2
Esterase	Pig liver	Sigma	1.0
Lipase	*Chromobacterium viscosum*	Asahi	Conversion < 10%*
Lipase	*Pseudomonas* sp.	Boehringer Mannheim	Conversion < 10%*
Lipase	Porcine pancreas	Boehringer Mannheim	Conversion < 10%*
Lipase	*Humicola sp.*	Boehringer Mannheim	Conversion < 10%*

No activity was found using the following enzymes: Lipase from *P. cepacia* and lipase G from *Pen. camembertii* (Amano), lipase from *P. fluorescens* (Biocatalysts), lipase from Porcine pancreas (Fluka), lipase from *M. miehei* (Lipozym IM, Novo), lipase from *C. antarctica* (Novozym 435, Novo), lipases from *Burkholderia* sp., *C. antarctica*, fraction B and from *M. miehei* (Boehringer Mannheim).
* At this conversion no enantiomeric ratio *E* could be calculated.



(S)-**1** (R)-**1** (S)-**2** (R)-**1**

Scheme 1. Reaction scheme for the enzyme catalysed enantioselective hydrolysis of *RS*-4-acetoxy-[2.2]paracyclophane.

room temperature. After centrifugation samples of the organic phase were taken and analysed by thin-layer and gas chromatography.

2.3. Thin layer and chiral gas chromatography

The determination of conversion and enantiomeric excess of **2** was carried out as described previously [5]. Separation using GC was slightly modified and carried out at a pressure of 0.8 kPa. The separation factor α was calculated to be 1.08. Retention times: *RS*-**1**: 10.8 min; *R*-**2**: 19.5 min; *S*-**2**: 21.1 min. Using TLC, the following migrations were determined: Rf(1) = 0.67; Rf(2) = 0.36.

3. Results and discussion

Using commercially available enzymes the synthesis of enantiomerically pure 4-hydroxy-[2.2]paracyclophane **2** using transesterification, esterification and hydrolysis reactions was investigated. Transesterification of *RS*-**2** using butyric or oleic acid and esterification reactions of 4-acetoxy-[2.2]paracyclophane **1** with vinylacetate, isopropenylacetate, vinylbutyrate or vinylcaproate completely failed. In contrast the enzymes listed in Table 1 were found to hydrolyse *RS*-**1** (Scheme 1) to preferentially the *S*-enantiomer of **2**. Whereas most of the enzymes showed low to moderate enantioselectivity, with *C. rugosa* lipase (CRL) an enantiomeric excess of 99.5% was obtained after 65% conversion, corresponding to an enantiomeric ratio $E = 20$.

Because of the low solubility of **1** the screening was carried out using a biphasic system containing toluene as a cosolvent. The enantiomeric excess was measured by chiral gas chromatography at different conversions of each reaction carried out. The enantiomeric ratio E was calculated according to Chen and Sih [10].

Presently we are optimising the reaction conditions for the CRL catalysed synthesis of *R*-**1**. Although it is possible to synthesise preparative amounts of *R*-**1** using the screening conditions described above, a higher enantiomeric excess at 50% conversion is desirable to overcome the major drawbacks of alternative methods, i.e., low yields, to a greater extent.

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