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Desymmetrization of *meso*-Hydrobenzoin *via* Stereoselective Enzymatic Esterification

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Abstract: Desymmetrization of *meso*-hydrobenzoin by irreversible acyl transfer using vinyl acetate as the acyl donor in the presence of *Rhizopus javanicus* lipase or *Candida cylindracea* lipase enables the preparation of (*R*)-1-acetoxy-(*S*)-2-hydroxy-1,2-diphenylethane and (*S*)-1-acetoxy-(*R*)-2-hydroxy-1,2-diphenylethane respectively in excellent optical purity.

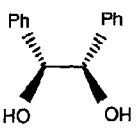
INTRODUCTION

Biocatalysed methodology has in recent years become one of the most proficient routes to optically pure molecules. In particular, the ability of lipases for differentiation between enantiomeric alcohols (and esters) is now well documented.[1a-d]

Lipase-catalysed enantiospecific transesterification has been exploited not only in the resolution of racemates of a number of monohydric alcohols, but also of many diols, among which some *vic*-diols.[2a-e] On the contrary, only few *meso*-form of *vic*-diols have been desymmetrized through biocatalysed stereoselective esterification,[2c,d] a procedure thas has the advantage of transforming, in principle, 100% of the starting material into the desired homochiral product. Enantiomerically pure compounds thus obtained can then be elaborated to afford a variety of optically active products. For instance, they can be converted *via* oxidation into α-hydroxyketones, versatile building blocks in organic synthesis or, *via* replacement of the unprotected secondary alcohol function with an amino group, into amino alcohols potentially valuable as chiral auxiliares for asymmetric synthesis.[3] The ready availability of *meso*-hydrobenzoin (1,2-diphenyl-1,2-ethanediol, **1**) prompted us to consider this diol as substrate in lipase-catalysed transesterification, and we wish to describe here the results obtained.

METHODS AND RESULTS

In the early stage of the present study many lipases, including lipases from *Candida cylindracea, Pseudomonas cepacia, Aspergillus niger, Rhizopus javanicus, Mucor javanicus* and porcine pancreatic lipase have been tested in the irreversible transesterification of **1** with vinyl acetate in the organic solvent system, cyclohexane-*tert*-amyl alcohol. Of these enzymes, only lipases from *Candida cylindracea* (CCL) and *Rhizopus javanicus* (RJL) were active. ^{1}H-NMR spectroscopy also in the presence of Eu(hfc)$_3$ evidenced that the transesterification product was a monoacetate of good optical purity but with opposite stereochemistry using one or the other lipase. At this point, further experiments were carried out with both CCL and RJL in different solvents, and the results are summarised in Table 1.



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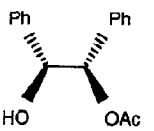
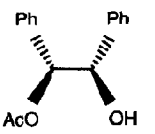


2a



2b

The very polar acetonitrile gave poor results with both enzymes. Among the solvent systems screened, cyclohexane-*tert*-amyl alcohol was the best, in terms of chemical yield and ee, when RJL was used as catalyst, while toluene was the most effective in improving yields and enantioselectivity in the reaction catalysed by CCL. A kinetic investigation showed that the reaction profile is almost linear when RJL is the catalyst. Conversely, when CCL is used the reaction occurs rapidly in the initial stage reaching about 30% conversion in *ca.* 3 h, and is followed by a second stage, in which the reaction comes to a near standstill, due to product inhibition (Figure 1).

A preparative run with RJL was carried out employing an amount of enzyme fourfold that used in the preliminary experiments, and was quenched after 24 h. Column chromatography on Si Diol (the use of Si gel proved to be detrimental, causing extensive racemization) gave a monoacetate (isolated yield 70%) with excellent optical purity (ee 90%). Its absolute configuration was determined as (*R*)-1-acetoxy-(*S*)-2-hydroxy-1,2-diphenylethane **2a** by MnO_2 oxidation, that gave a product with the same optical rotation of the known *R*-benzoin acetate. Therefore the monoacetate obtained in the transesterification catalysed by CCL, which has stereopreference opposite to RJL, must be its enantiomer, (*S*)-1-acetoxy-(*R*)-2-hydroxy-1,2-diphenylethane, **2b**.

Taking into account that the reaction profile of the CCL-catalysed reaction indicates a maximum conversion near 30%, we tried to prepare **2b** by treatment of *meso*-hydrobenzoin diacetate with *n*-butanol in the presence of RJL, since enzymatic alcoholysis is stereochemically

complementary to enzymatic esterification. As this attempt was unsuccessful, we reconsidered the CCL-catalysed reaction. At the end of a first run (incubation period 3 h) the enzyme was recovered by filtration, washed with toluene and recycled in four successive turnovers, with about 5% of total enzyme activity loss. Column chromatography of the pooled filtrates from the five runs gave **2b** in 28% yield (ee 90%) along with *ca.* 65% of unconverted diol, directly recyclable.

Table 1. Enzyme-catalysed Desymmetrization of *meso*-Hydrobenzoin[a]

Enzyme	Solvent	Time, h	Yield[b],%	Stereopreference	ee, %[c]
RJL	Cyclohexane-*t*-amyl alcohol[d]	48	20	*R*	90
	Vinyl Acetate	48	19	*R*	80
	Toluene	48	23	*R*	78
	Acetonitrile	48	3	nd[e]	nd[e]
CCL	Cyclohexane-*t*-amyl alcohol[d]	24	9	*S*	80
	Vinyl Acetate	24	7	*S*	>98
	Toluene	24	28	*S*	90
	Acetonitrile	24	0.2	nd[e]	nd[e]

[a] Substrate 5 mg/mL, vinyl acetate 50 μL/mL (if not used as solvent), lipase 50 mg/mL. [b] Determined by GC analysis. [c] Determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$. [d] Ratio 9:1. [e] not determined.

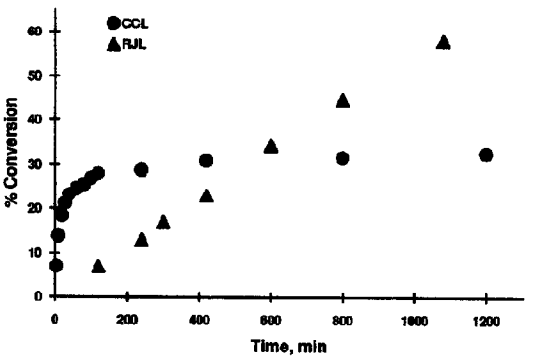


Figure 1. Reaction profile for the esterification in toluene of *meso*-hydrobenzoin catalysed by lipase from *C. cylindracea* (CCL) or *R. javanicus* (RJL) (see Experimental).

We wish to remark here that no formation of diester was observed in the transesterification of **1** catalysed by CCL or RJL. In our opinion this is to be ascribed more to steric hindrance, due to the acyl group in the monoester, than to the high stereoselectivity of these lipases. This contention is supported by: i) the observed inertness of *meso*-hydrobenzoin diacetate to the attempted alcoholysis catalysed by CCL or RJL, and ii) the observation that racemic hydrobenzoin by irreversible acylation with vinyl acetate in the standard conditions gives (*R*)-1-acetoxy-(*R*)-2-hydroxy-1,2-diphenylethane in the presence of RJL and its enantiomer, (*S*)-1-acetoxy-(*S*)-2-hydroxy-1,2-diphenylethane, in the presence of CCL, without formation in both cases of the corresponding diacetate.[4]

EXPERIMENTAL SECTION

General.

Meso- and (±)-hydrobenzoin were purchased from Aldrich Chemicals. Lipases from *Candida cylindracea*, *Pseudomonas cepacia*, *Aspergillus niger* (AP6), *Rhizopus javanicus* and *Mucor javanicus* (M-10) were from Amano International Enzyme Co. Lipase from porcine pancreas was obtained from Sigma. All the enzymes were dried under vacuum overnight prior to use. Solvents were dried over 3Å molecular sieves. Vinyl acetate was distilled prior to use. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ (tetramethylsilane as internal reference) on a Bruker AC-250 instrument at 250.13 and 62.9 MHz, respectively. Europium(III) tris[3-(heptafluoropropyl)hydroxymethylene]-(+)-camphorate], [Eu(hfc)$_3$], was used as chiral shift agent. IR spectra were registered on a Perkin Elmer 1720X FT-IR spectrophotometer. Optical rotations were measured on a Jasco DIP-370 polarimeter.

GC analyses were carried out on a HP-5 5% phenylmethylsilicone capillary column. Preparative column chromatography, unless otherwise stated, was performed on 40-63 μm LiChroprep Si Diol.

Standard procedure for lipase-mediated esterification of 1.

Diol **1** (5 mg/mL; 23 mM) was dissolved in the solvent of choice (Table 1) containing vinyl acetate (50 μL/mL). Enzyme (50 mg/mL) was added and the suspension shaken at 45 °C. After the given time the enzyme was removed by filtration and the filtrate evaporated and analysed by GC for the determination of the conversion. Enantiomeric purities were determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$ using the integrated areas of the acetoxy resonances. Reactions for kinetic investigation were performed in toluene using 200 mg/mL of lipase. Values of % conversion are mean values of three GC determinations.

Preparation of (R)-1-acetoxy-(S)-2-hydroxy-1,2-diphenylethane **2a**.

To a solution of **1** (50 mg; 0.234 mmol) in cyclohexane-*t*-amyl alcohol (9:1 vol/vol; 10 mL) vinyl acetate (0.5 mL) and lipase from *R. javanicus* (2 g) were added. After 24 h the enzyme was filtered off, the solvent evaporated and the residue subjected to column chromatography (ethyl acetate/petrol ether as eluent) to afford **2a** (40 mg, 70% yield, 90% ee) as white powder. Recrystallized from hexane it had mp 79-80 °C; $[\alpha]_D$ = -5.1 (*c* 0.65, benzene). IR (CCl_4) 3466, 3067, 3035, 2931, 1749, 1455, 1372, 1234, 1029 cm^{-1}. ^{1}H-NMR δ 2.00 (s, 3H, -OAc), 2.12 (d, 1H, J= 3.6 Hz, OH), 5.0 (dd, 1H, J=6.0 and 3.6 Hz, -C*H*OH), 5.90 (d, 1H, J=6.0 Hz, -C*H*OAc), 7.28 (m, 10H, -Ar). ^{13}C-NMR δ 20.97, 76.24, 78.83, 126.88, 127.67, 128.05, 128.20, 128.37, 136.35, 139.52, 169.76.

Determination of absolute configuration of **2a**.

A suspension of MnO_2 (100 mg) in a solution of **2a** (50 mg, 90% ee) in CH_2Cl_2 (5 mL) was shaken at room temperature for 24 h. The reaction mixture was filtered and the filtrate taken to dryness in vacuo. The residue was purified by Si gel chromatography to afford 45 mg of (*R*)-acetoxybenzoin $[\alpha]_D$ = -210.0 (*c* 0.5, benzene), lit.[5] $[\alpha]_D$ = -230.5 (*c* 1, benzene).

Preparation of (S)-1-acetoxy-(R)-2-hydroxy-1,2-diphenyletane **2b**.

To a stirred solution of **1** (10 mg, 0.047 mmol) in toluene (2 mL) containing vinyl acetate (100 µL) at 45°C crude CCL (400 mg) was added. After 3 h the enzyme was recovered by filtration, washed with toluene and used in a second run in the same conditions. The recycling of the enzyme was repeated for a total of five successive runs. The combined filtrates and washings from the five runs were evaporated and the residue purified by column chromatography to give **2b** (17 mg, 28% yield, 90% ee), $[\alpha]_D$ = + 5.0 (*c* 0.7, benzene) and unreacted **1** (32 mg; 64% yield). The total loss of enzyme activity (determined as conversion of substrate) after five turnovers was about 5%.

Attempt to synthesise **2b** *by transesterification between* meso-*hydrobenzoin diacetate and n-butanol*.

A solution of *meso*-hydrobenzoin diacetate (50 mg; 0.168 mmol) and *n*-butanol (250 µL) in cyclohexane-*t*-amyl alcohol (9:1 vol/vol; 10 mL) was shaken at 45°C in the presence of lipase from *R. javanicus* (2 g). No deacetylated product formation was observed throughout 4 days of incubation.

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REFERENCES AND NOTES

1. For recent reviews see: a) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. b) Faber, K. and Riva, S. *Synthesis* **1992**, 895. c) Santaniello, E.; Ferraboschi, P. and Grisenti, P. *Enzyme Microb. Technol.* **1993**, *15*, 367. d) Boland, W.; Frößl, C. and Lorenz, M. *Synthesis* **1991**, 1049.

2. a) Seemayer, R. and Schneider, M. P. *J. Chem. Soc., Chem. Commun.*, **1991**, 49. b) Bhattacharya, A. and Ali, E. *Indian J. Chem.*, **1992**, 898. c) Mattson, A.; Öhrner, N.; Hult, K. and Norin, T. *Tetrahedron: Asymmetry* **1993**, *4*, 925. d) Bisht, K.S.; Parmar, V. S. and Crout, D. H. G. *Tetrahedron: Asymmetry* **1993**, *4*, 957. e) Caron, G. and Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1995.

3. Mi, A.Q.; Wang, Z.Y. and Jiang, Y. Z. *Tetrahedron: Asymmetry* **1993**, *4*, 1957.

4. Racemic hydrobenzoin (50 mg; 0.23 mmol) was dissolved in toluene (10 mL) and vinyl acetate (0.5 mL) and enzyme (RJL or CCL; 2 g) were added. At the end of incubation period (60 h with RJL and 24 h with CCL) the enzyme was filtered off and the filtrate taken to dryness. The residue was separated by Si gel chromatography to give (*R*)-1-acetoxy-(*R*)-2-hydroxy-1,2-diphenylethane [42% yield, ee >98%, $[\alpha]_D$ +10.1 (*c* 0.5, $CHCl_3$)] in the reaction catalysed by RJL, and (*S*)-1-acetoxy-(*S*)-2-hydroxy-1,2-diphenylethane [30% yield, ee >98%, $[\alpha]_D$ -10.0 (*c* 0.4, $CHCl_3$)] in the reaction catalysed by CCL.

5. Enders, D. and Bhushan, V. *Tetrahedron Lett.* **1988**, *29*, 2437.

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