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'Gelozymes' in organic synthesis. Part 2: *Candida rugosa* lipase mediated synthesis of enantiomerically pure (*S*)-cyano(3-phenoxyphenyl)methyl butyrate†

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Abstract—Significant changes in enantioselectivity (E) have been observed when the butanoate ester of (±)-1-hydroxy-1-(3-phenoxyphenyl)acetonitrile was subjected to hydrolysis in acetate buffer (pH 4.5, $E=6.4$) and alcoholysis with 1-butanol in hexane catalysed by *Candida rugosa* lipase ($E=45$). Enantiomerically pure (*S*)-butanoate ester so obtained (e.e. 98.4%) was converted to the corresponding (*S*)-cyanohydrin using *Pseudomonas cepacia* (Amano Ps) gelozyme. This strategy overcomes the problem of separation of the unwanted (*R*)-ester from the (*S*)-cyanohydrin.

1. Introduction

The cyanohydrin, (*S*)-2-hydroxy-(3-phenoxy) phenylacetonitrile **4**, is an important intermediate in the production of highly potent synthetic pyrethroids such as Cypermethrin and Esfenvalerate. Several enzymatic approaches have been developed for the synthesis of enantiomerically pure cyanohydrins.[1] These can be classified into two types of approaches. The first approach is based on the enantioselective addition of HCN to 3-phenoxybenzaldehyde catalysed by enzyme oxynitrilase from *Sorghum bicolor* or *Haevea brasiliens* by direct addition[2,3] or transcyanation.[4] The second approach is based on lipase-catalysed enantioselective hydrolysis[5] or alcoholysis[6–8] of racemic cyanohydrin ester using an (*S*)-specific lipase to obtain a mixture of (*R*)-ester and (*S*)-cyanohydrin. The (*R*)-ester is then separated from the (*S*)-cyanohydrin by solvent extraction[6] or distillation under very high vacuum,[7] racemised by treatment with a base and recycled. In continuation of our work on the chemo-enzymatic preparation of (*S*)-**4**,[8] we found that the solvent extraction process as described by Fishman and Zviely[6] needs to be very efficient to avoid contamination of the product with (*R*)-ester, while vacuum distillation at very low pressure (0.001 Torr) was energy intensive. It was thus necessary to devise an alternate methodology.

From the literature data it was found that lipase from *Candida rugosa* (CRL) is selective towards the (*R*)-esters of 2-hydroxy-(3-phenoxy) phenylacetonitrile[9] and it occurred to us that a strategy involving two enzymatic steps could be devised. In the first step the (*RS*)-cyano(3-phenoxyphenyl)methyl butyrate **1** would be subjected to enantioselective alcoholysis of the (*R*)-ester to (*R*)-cyanohydrin-**3** catalysed by *C. rugosa* lipase in hexane. The (*R*)-cyanohydrin being unstable under these conditions would decompose to 3-phenoxybenzaldehyde on treatment with 1 M imidazole solution and can be removed from reaction mixture by distillation under vacuum (bp 90–92°C at 0.1 mm). In the second enzymatic step the (*S*)-ester-**2**, which is obtained with high enantiomeric purity, can then be subjected to alcoholysis with 1-butanol in hexane catalysed by Ps Amano gelozyme. The cyanohydrin (*S*)-**4** so obtained in high chemical and enantiomeric purity can then be coupled with an appropriate acid chloride to obtain the desired pyrethroid such as Esfenvalerate (Scheme 1). Such a strategy would nullify the need to separate the (*R*)-ester and the (*S*)-cyanohydrin.

Herein, we present details of our results on the preparation of (*S*)-cyano(3-phenoxyphenyl)methyl butyrate by CRL-catalysed reaction using the racemic ester (±)-**1**.[10] We have observed that the enantioselectivity of the hydrolytic reaction in acetate buffer is very low ($E=6.4$, pH 4.5) but it can be greatly improved by carrying out the alcoholysis with 1-butanol in hexane ($E=45$).

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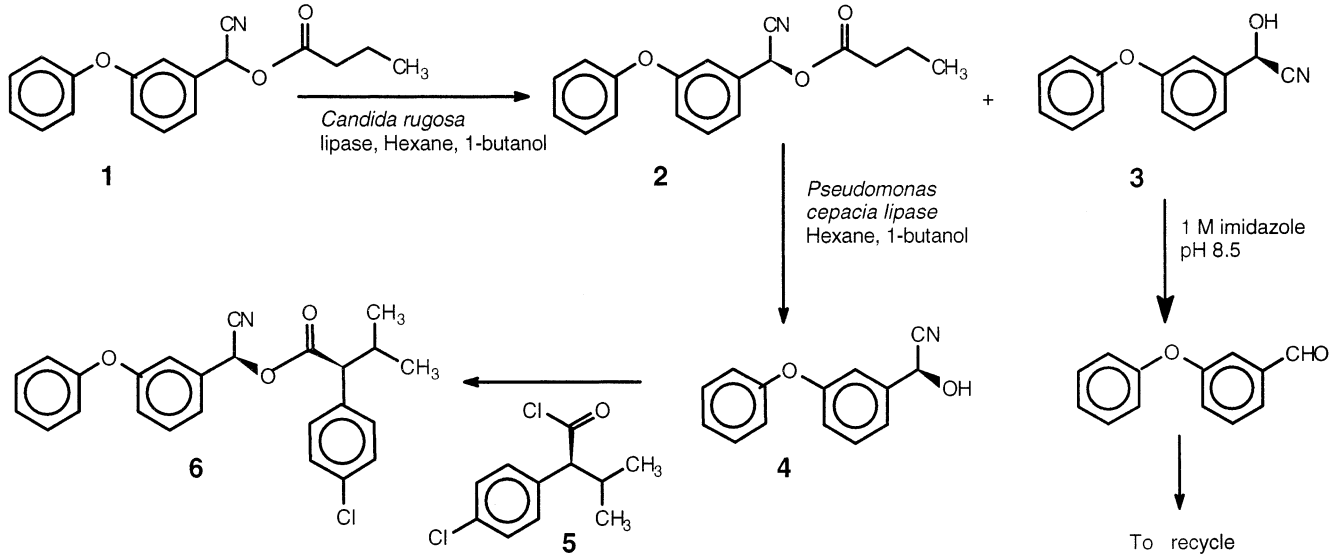

Scheme 1.

2. Results and discussion

2.1. Hydrolysis of (*RS*)-cyano(3-phenoxyphenyl)methyl butyrate 1 in aqueous buffer

C. rugosa lipase-catalysed hydrolysis of **1** in 0.05 M acetate buffer at pH 4.5 proceeds readily with (*R*)-selectivity, but with low enantioselectivity ($E=6.4$). This was even lower than the value of $E=12$ reported by Mitsuda et al. for CRL-catalysed hydrolysis of the corresponding acetate ester.[9] Commercially available lipase actually consists of at least two distinct lipases I and II.[11–15] Kazlauskas et al. demonstrated that a simple 2-propanol treatment can increase the enantioselectivity of crude lipase to a considerable extent. We have repeated the experiments of Kazlauskas[15] and obtained two forms of *C. rugosa* lipase, one soluble and the other insoluble in an *iso*-propanol–water mixture. The soluble fraction on dialysis and freeze drying gave an enzyme preparation which hydrolysed standard lipase substrate tributyrin at a rate twice as fast as the commercial sample, but did not hydrolyse the butanoate ester **1**. The insoluble fraction was less reactive towards tributyrin (50% activity) but hydrolysed the butanoate ester **1**. Unfortunately we did not find any improvement in enantioselectivity using this precipitated enzyme preparation.

Chen and Sih[16] suggested examining the esterification mode in organic solvents when hydrolytic reaction in aqueous media proceeds with poor enantioselectivity. It was thus considered prudent to explore the possibilities of obtaining better resolution with CRL-catalysed alcoholysis in a water-immiscible organic solvent.

2.2. Enantioselective alcoholysis of (*RS*)-cyano(3-phenoxyphenyl)methyl butyrate 1 with *Candida rugosa* lipase

2.2.1. Effect of solvent on enantioselectivity and reaction rate. Various solvents such as chloroform, dichloromethane, ethylacetate, di-*iso*-propyl ether, hexane, heptane and *iso*-octane were used for the lipase-catalysed alcoholysis reaction with 1-butanol (3 equiv.) as the nucleophile. We observed that the reactions were extremely slow in chloroform, dichloromethane and ethylacetate. Di-*iso*-propyl ether and hydrocarbon solvents like hexane, heptane and *iso*-octane were found to be suitable. Hexane was chosen as a solvent for further studies.

2.2.2. Effect of alcohol acyl acceptor on enantioselectivity. It has been noted earlier that the carbon chain length of the alcohol affects the enantioselectivity of lipase-catalysed reactions.[1,17] To optimise the reaction conditions, the alcoholysis reactions were carried out under identical conditions with alcohols of varying chain length and the results are summarised in Table 1. It can be seen that the best results are obtained with 1-butanol as the acyl acceptor. This is in agreement with the earlier observations with *Pseudomonas* lipase.[6–8]

2.2.3. Effect of 1-butanol concentration on enantioselectivity *E*. We have observed a significant effect of 1-butanol concentration not only on the reaction rate but also on the enantioselectivity of the reaction. Table 2 gives the results of our observations. It can be seen that both the enantioselectivity and the rate of reaction (% conversion) reach an optimum when the substrate to alcohol molar ratio was 3. It is very interesting to note that the value of enantioselectivity (E) increases from 13 at a molar ratio of substrate to alcohol of 0.5 to $E=48$ when 3 molar equivalents of alcohol were used. It is possible that a conformational change occurs in the enzyme by action of 1-butanol in hexane, which is responsible for the results in Table 2. To confirm this possibility, the enzyme recovered after alcoholysis reaction was used for the hydrolytic reaction in acetate buffer. The (E) value of the recovered lipase ($E=6.4$) was unchanged. This indicated that the increased enantioselectivity during alcoholysis in hexane was not due to a permanent conformational change in the enzyme.

Table 1. Effect of acceptor alcohol on enantioselectivity of CRL-catalysed alcoholysis of (*RS*)-**1**[a]

S. no	Alcohol	Conversion (%)	% e.e. of (*S*)-ester
1	Methanol	29	25
2	Ethanol	40	42.5
3	1-Propanol	42	64.8
4	2-Propanol	45	41.2
5	2-Chloroethanol	32	42.7
6	1-Butanol	54	98
7	2-Methyl-1-propanol	49	76.5
8	*tert*-Butanol	44	55.2
9	1-Pentanol	46	64.6
10	1-Hexanol	70	89
11	1-Heptanol	58	88
12	1-Octanol	63	70.6

[a] Reactions were carried out using (*RS*)-butyrate **1** (295 mg, 1 mmol) in hexane (20 mL) containing alcohol (3 mmol) and lipase (100 mg) at 25°C for 8 h. (Experiments were repeated with different batches of enzyme obtained from two different sources Sigma, USA and Fluka, Switzerland with consistent results.)

This was further confirmed by using the insoluble lipase fraction obtained by treatment with *iso*-propanol. It was found that this lipase fraction hydrolyses the (±)-**1** in acetate buffer with $E=6.4$ and when used for alcoholysis reactions gives results similar to those in Tables 1 and 2. Clearly, treatment of the crude enzyme by *iso*-propanol was of no advantage. Although it has been noted earlier, in cases of alcoholysis reactions with *Pseudomonas cepacia* lipase where the concentration of alcohol changes the enantioselectivity and rate of alcoholysis reaction[6,7] the effects are not as dramatic as observed by us.

Table 2. Effect of alcohol concentration on enantioselectivity of CRL-catalysed alcoholysis of (*RS*)-**1**[a]

[Ester]/[1-butanol]	Enantioselectivity (*E*)	Conversion (%)
0.5	13	34
1.0	19	35
1.5	22	43
2.0	38	47
3.0	48	54
4.0	41	40
6.0	20	41
8.0	15	33
10	13	25

[a] Reactions were carried out using (*RS*)-butyrate **1** (295 mg, 1 mmol) in hexane (20 mL) containing 1-butanol (varying amounts) and lipase (100 mg) at 25°C for 8 h. *E* was calculated according to the method of Sih.[18]

2.2.4. Effect of substrate concentration on enantioselectivity. The data in Table 2 is based on rather low substrate concentration (1.5%). For a large scale process, it is desirable that the substrate concentration is much higher. However, an increase in substrate concentration is accompanied by a parallel increase in the amount of alcohol in given volume and this could affect the enantioselectivity of the reaction, as well as the stability of the enzyme. It was thus important to find out the effect of substrate concentration on the enantioselectivity of the alcoholysis reaction. In these experiments, the enzyme to substrate ratio (w/w) was kept constant at 1:3 to avoid too many variables. It was observed that the overall rate of the reaction (amount of ester reacted/h/g enzyme) increases with substrate concentration and the enantioselectivity *E* was not substantially affected. However, the data did not fit into a standard Michaelis–Menten kinetic equation, probably due to change of alcohol concentration of the medium which would affect enzyme–substrate binding (Table 3).

2.2.5. Enantioselective alcoholysis of (*RS*)-cyano(3-phenoxyphenyl)methyl butyrate 1 with *Candida rugosa* lipase immobilised in gelatin matrix. Our previous experience with gelozymes of *C. rugosa* lipase[19] and Amano Ps lipase[8] prompted us to explore the possibility of using the enzyme in immobilised form for the alcoholysis reaction. Thus, alcoholysis of **1** was carried out using 3 molar equivalents of 1-butanol in hexane. However, this time the immobilised enzyme showed enantioselectivity $E=12.5$, which was higher than that for hydrolysis in aqueous buffer but much lower than that for the reaction using the free enzyme powder. When the gelozyme was thoroughly freeze dried, the alcoholysis reaction was extremely sluggish and the presence of a small quantity of bound water was necessary for the reaction to occur at a workable rate. Although the amount of bound water was found to have a strong influence on enantioselectivity, it was difficult to control the amount of bound water over long periods and

Table 3. Effect of substrate concentration on enantioselective alcoholysis of (*RS*)-cyano(3-phenoxyphenyl)methyl butyrate **1** with 1-butanol in hexane catalysed by *Candida rugosa* lipase[a]

[*RS*-**1**] (mM)	% e.e. of (*S*)-**2**	% e.e. of (*R*)-**3**	Conversion (%)	*E*	Reaction rate (μM/h/mg)
33.9	32.8	94.5	26	49	16.6
67.8	40.6	94.0	30	48	19.1
101.7	42.9	93.5	31	45	19.7
135.6	66.6	91.5	42	45	26.7
169.5	93.5	93.5	52	46	33.1

[a] Reactions were carried out using (*RS*)-butyrate **1** in hexane containing 1-butanol and lipase at 25°C for 8 h. [1-Butanol]/[1] = 3; reaction volume 20 mL. Rates are given as micromoles/litre of product formed per hour, per mg of enzyme powder. Product concentrations are based on chiral HPLC analysis.

obtain consistent results due to the hygroscopic nature of the gelozyme.

Based on the above results, the alcoholysis reaction was carried out using free enzyme powder in hexane with a substrate:enzyme ratio of 3:1 (w/w) and a molar ratio of substrate to alcohol of 1:3. The reaction was carried out at 25°C in a stirred tank and was followed by chiral HPLC until the e.e. of the unreacted (*S*)-ester was >98% (approx. 60% conversion, 8–9 h). The reaction was then stopped and the enzyme powder was filtered for recycling. The reaction mixture was stirred with 1 M aqueous imidazole at pH 8.5 to decompose the cyanohydrin, forming 3-phenoxybenzaldehyde without racemisation of the (*S*)-ester. The aldehyde and butyl butanoate were removed from the reaction mixture by distillation under vacuum at a temperature lower than 100°C. The (*S*)-ester was unaffected under these conditions. The recovered (*S*)-ester was then dissolved in hexane and subjected to alcoholysis catalysed by *P. cepacia* gelozyme as described earlier.[8a] The hexane solution after alcoholysis contains 1-butanol, acetic acid and butyl butanoate along with the (*S*)-cyanohydrin (e.e. >99%). The butanol and acetic acid impurities were removed simply by extracting the hexane layer with cold aqueous acetate buffer (0.01 M, pH 4.0). Analysis of the dried hexane layer at this stage by chiral HPLC showed less than 1% decomposition of the cyanohydrin to aldehyde. The (*S*)-cyanohydrin **4** was then coupled with 2-(4-chlorophenyl)-3-methyl-(2*S*)-butanoyl chloride **5** (e.e. 97%) in the presence of pyridine to obtain a mixture of Esfenvalerate and butyl butanoate along with small quantities of unreacted (*R*)-ester and 3-phenoxybenzaldehyde. This mixture was easily purified by column chromatography to obtain pure Esfenvalerate **6** (d.e. 96%) in 65% overall yield based on (±)-**1**. Considering the 97% e.e. of 2-(4-chlorophenyl)-3-methyl-(2*S*)-butanoic acid, the observed d.e. of 96% indicates that enantiomeric purity of the (*S*)-cyanohydrin **4** was not seriously affected during these operations. The recovered aldehyde can be re-used in the preparation of the butanoate ester **1**. The free enzyme powder of *C. rugosa* could be recycled five times without serious loss of activity, but the activity decreased with further recycles and had only 50% of its original activity after ten recycles.

3. Conclusion

In conclusion, the work presented has shown that it is possible to obtain products of improved enantioselectivity by changing the mode of reaction (hydrolysis→ alcoholysis). Differences in enantioselectivities of hydrolytic versus alcoholysis/esterification reactions have been known earlier and thermodynamic considerations attribute this to a partial loss of specificity due to high concentration of water in aqueous solutions,[16] this also appeared to be the reason in the present case. Our methodology overcomes the major problem of separation of cyanohydrin and unreacted ester in the preparation of Esfenvalerate in 65% overall yield in high enantiomedric purity (e.e. >98%) and high diastereomeric purity (d.e. 96%). The aldehyde can be recovered and recycled and hence there is no net loss of expensive raw materials. The sequence of enzymatic reactions can be altered according to the required stereochemical configuration of the cyanohydrin.

4. Experimental

Lipase from *C. rugosa* was obtained from Sigma, USA (Type VII, 875 units/mg), and Fluka AG Switzerland (cat. no. 62316). Lipase Ps was obtained from Amano Pharmaceutical Corporation Ltd., Japan. All other reagents were A.R. grade obtained from SD Fine Chem, India. HPLC analyses were carried out on Hewlett Packard HP1090 unit with diode array detector and HP Chem station. (*RS*)-Cyano(3-phenoxyphenyl)methyl butyrate **1** was prepared and chiral HPLC analysis was performed as reported earlier.[8a]

4.1. Enzymatic preparation of (*S*)-2

(*RS*)-**1** (2.95 g, 10 mmol) in hexane (60 mL) and 1-butanol (2.23 g, 30 mmol) were stirred magnetically with *C. rugosa* lipase (1 g) in a round bottom flask. The progress of the reaction was monitored by chiral HPLC. The reaction was continued until all (*R*)-ester was consumed (8–9 h, 60% conversion). The reaction mixture was then filtered through a sintered buchner funnel and the filtrate was stirred with aqueous imidazole solution (1 M, pH 8.5) for 1 h to decompose the cyanohydrin to 3-phenoxybenzaldehyde. The reaction mixture was then separated, concentrated and subjected to Kugelrohr distillation under vacuum (0.1 mm) to remove butylbutanoate and 3-phenoxybenzaldehyde, while keeping the temperature below 100°C. The residue, which consisted of >98% (*S*)-ester (HPLC analysis) was purified by column chromatography using hexane as eluent (1.03 g, 70% of theoretical). $[\alpha]_D^{25} = +4.9$ (*c* 1, chloroform), e.e. = 98.4%; lit.[6] $[\alpha]_D^{25} = -8.1$ (*c* 1, chloroform) for the (*R*)-acetate.

The purified (*S*)-ester (1.03 g, 3.4 mmol) was dissolved in hexane (20 mL), 1-butanol (740 mg, 10 mmol) was added along with glacial acetic acid (50 μL) and the reaction mixture was stirred with lipase from *P. cepacia* (Amano Ps gelozyme, 1.5 g, 300 mg enzyme) for 3 h at room temperature. When all of the butanoate ester was converted to (*S*)-cyanohydrin, the enzyme was filtered, and the hexane solution of the (*S*)-cyanohydrin was stored in refrigerator for further reactions.

4.2. Enzymatic preparation of (*S*,*S*)-6

The reaction mixture obtained as above was extracted with acetate buffer (0.01 M, pH 4.0) in ice-cold conditions (3×10 mL) and the organic layer was dried over anhydrous $CaCl_2$ overnight in a refrigerator. 2-(4-Chlorophenyl)-3-methyl-(2*S*)-butanoyl chloride **5** (810 mg, 3.5 mmol, e.e. = 97%) in hexane (5 mL) and pyridine (276 mg, 3.5 mmol) were added slowly over 30 min in the cold. The reaction mixture was then stirred overnight in the cold, washed with 10% sodium carbon-

ate (2×5 mL), aqueous HCl (1N, 2×5 mL) brine (1×5 mL) and dried over anhydrous magnesium sulfate. The organic layer was then concentrated on a rotavapor and the oily residue was chromatographed over silica gel using 15:1 hexane–ethyl acetate. Pure Esfenvalerate was obtained as an oil, which solidified to a white powder on standing in a refrigerator (1.35 g, 95% based on (*S*)-2), mp 42°C; d.e. 96%. $[\alpha]_D^{25}=-10.8$ (*c* 6.5, chloroform); lit.[20] $[\alpha]_D^{25}=-11.2$ (*c* 6.5, chloroform), d.e. 96%. ^{1}H NMR ($CDCl_3$) δ 6.9–7.4 (m, 13H), 6.28 (s, *S*,*R*, minor), 6.32 (s, *S*,*S*, major, 1H), 3.24 (d, 1H, $J=10.68$ Hz), 2.23–2.44 (m, 1H), 1.05 (d, 3H, $J=6.55$ Hz), 0.74 (d, 3H, $J=6.74$ Hz). ^{13}C NMR δ 171.43, 158.15, 156.22, 135.09, 133.06, 133.33, 130.58, 129.96, 129.76, 128.85, 124.06, 121.98, 120.24, 119.29, 117.50, 115.47, 62.65, 58.71, 32.03, 21.09, 19.98. Mass: 419 (M^+).

4.3. Chiral HPLC analysis

Enantiomeric purity of 2-(4-chlorophenyl)-3-methyl-(2*S*)-butanoic acid (e.e. 97%) was determined by chiral HPLC on Chiralcel OD column (5×250 mm), Diacel Chemical Industries, Japan. Mobile phase 1.25% *iso*-propanol in hexane containing 0.1% trifluoroacetic acid; flow rate 0.5 mL/min; detection wavelength 240 nm; retention times (*R*)-acid 23.8 min, (*S*)-acid 25.4 min. Chiral HPLC analysis of Esfenvalerate was carried out on a Chiralcel OJ column (5×250 mm), Diacel Chemical Industries, Japan. Mobile phase 18% *iso*-propanol in hexane; flow rate 0.7 mL/min; detection wavelength 240 nm. The four diastereomers of commercial racemic fenvalerate were well separated with retention times 12.15, 17.21, 21.22 and 24.27 min. The sample of Esfenvalerate prepared in our laboratory showed a minor peak at 12.12 min (*S*,*R*) and a major peak (*S*,*S*) at 24.27 min with d.e. 96%.

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