Tetrahedron: Asymmetry Vol. 4, No. 5, pp. 813-822, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Kinetic Resolution Strategies II: Enhanced Enantiomeric Excesses and Yields for the Faster Reacting Enantiomer in Lipase Mediated Kinetic Resolutions.

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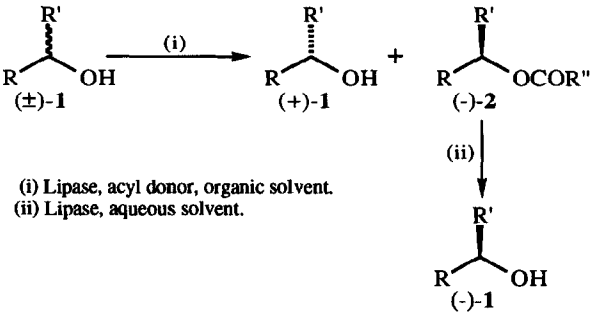
(*Received* 30 *March* 1993)

Abstract: A strategy for the preparation of the faster reacting (*R*)-enantiomer of 1-(4-methoxyphenyl)ethanol with 95% ee in 37% overall yield *via* a double kinetic resolution strategy involving *Pseudomonas fluorescens* lipase mediated sequential acetylation and hydrolysis is described.

Introduction:

In single kinetic resolution processes where the stereoselectivity factor (E) is moderate or low, if the slower reacting enantiomer of the substrate is required, high enantiomeric excesses (upto 100% ee) can still be obtained (at the expense of yield) by allowing the kinetic resolution to proceed to high conversions and isolating the recovered starting material. However, the maximum enantiomeric excess achievable for the faster reacting enantiomer (i.e the product from the kinetic resolution) is determined by the stereoselectivity factor and limited by mass action and can only be obtained by stopping the kinetic resolution at an infinitesimally small conversion, isolating the product and converting it back to the starting material. For a kinetic resolution that proceeds with a stereoselectivity factor (E) of, for example, 15, the maximum enantiomeric excess obtainable (for the faster reacting enantiomer) by this method is 87.5% [= 100 x (E-1)/(E+1)].

We have previously shown that enhanced product enantiomeric excesses and/or yields may be obtained for processes where both enantiomers of a chiral catalyst are available by the use of a double kinetic resolution strategy[1], as for example in Sharpless epoxidations or Noyori reductions. This strategy is not directly applicable to enzyme, e.g. lipase, mediated processes since only one enantiomer of the enzyme is available. An advantage of lipases however is that the reactions they catalyse (saponification/ esterification) are able to be reversed under appropriate conditions. This feature allows an alternative double kinetic resolution strategy to be employed (Scheme 1) in which the first kinetic resolution would be a lipase mediated esterification of a racemic alcohol **1**, and in the second kinetic resolution, the scalemic ester product **2** (from the first kinetic resolution) would be used as the starting material in a lipase mediated hydrolysis. If the same lipase was used in each step it was expected that in the second kinetic resolution, the enantiomer in which the ester **2** was enriched would be the faster reacting enantiomer. Isolated examples of this strategy have been reported[2] but the potential of the concept and benefits in enantiomeric excess and yield obtainable have not been widely exploited. The general strategy is illustrated in Scheme 1.



Scheme 1 : Proposed double kinetic resolution using lipase mediated reactions.

Results and Discussion:

Computer modelling of the proposed double kinetic resolution strategy (Scheme 1) indicated that it would enable preparation of the faster reacting enantiomer [represented by (-)-**1** in Scheme 1] with significantly improved yield and enantiomeric excess. This double kinetic resolution strategy (Scheme 1) should be viable in terms of allowing increased yields and/or enantiomeric excesses for those processes where the stereoselectivity factor is <50. However this is only the case when both the forward and reverse processes have similar stereoselectivity factors. Variation of the enantiomeric excess of the product from the second kinetic resolution with conversion is identical to that for the recycling strategy originally reported by Sih *et al.*[3] However, the present strategy is more economical in terms of the number of steps involved.

The enantiomeric excess of the final product from this double kinetic resolution depends on the stereoselectivity factors for the forward and reverse reactions and the extent of reaction for each step. Herein we illustrate the strategy for the case where both reactions proceed with the same stereoselectivity factor E = 15. The overall maximum theoretical yields *versus* the enantiomeric excess of the faster reacting enantiomer obtainable by this double kinetic resolution strategy (when E = 15 for each step) are compared graphically with the theoretical yields available by conventional single kinetic resolution methods (when E = 15) in the Figure.

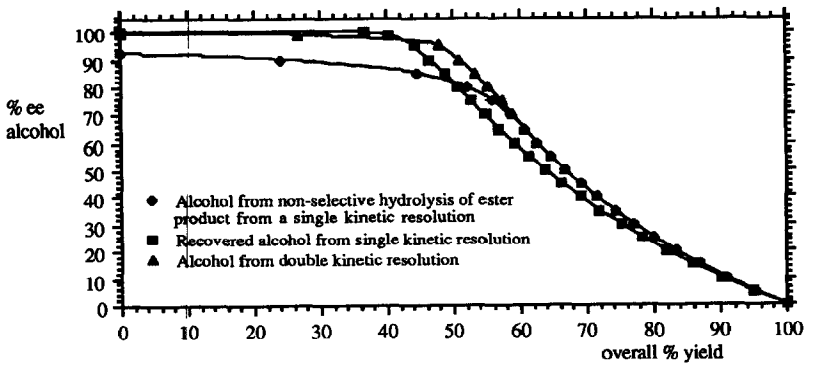


Figure : Comparison of theoretical yields of alcohol versus ee obtainable by conventional kinetic resolution methods with those obtainable by this double kinetic resolution strategy with E = 15 for both steps.

As can be seen from the Figure, the maximum enantiomeric excess for the faster reacting enantiomer using a single step kinetic resolution (when E = 15) is 87.5% (obtainable at an infinitesimally small conversion and therefore with an infinitesimally small yield). However the double kinetic resolution strategy described above can lead to the preparation of the faster reacting enantiomer of the substrate (-)-**1** with significantly enhanced enantiomeric excesses and yields. For example if the faster reacting enantiomer (-)-**1** with an enantiomeric excess of 95% is required, it would be impossible to obtain it in one kinetic resolution using a lipase that shows the stereochemical preference indicated in Scheme 1 (when E = 15). Whereas, using the double kinetic resolution, a theoretical yield of (-)-**1** with an ee = 95% of 42% can be achieved. The theoretical yield for the slower reacting enantiomer (+)-**1** with an ee = 95% obtainable from the first kinetic resolution is 39%. Table 1 compares the overall theoretical yield possible using this double kinetic resolution strategy for various enantiomeric excesses with the yields possible by conventional methods.

ee (%) required from kinetic resolution of racemic substrate **1**	Yield (%) of slower reacting enantiomer (+)-**1** from single kinetic resolution	Yield (%) of faster reacting enantiomer (-)-**1** from single kinetic resolution.[a]	Yield (%) of faster reacting enantiomer (-)-**1** from a double kinetic resolution.
75	50	49	57
80	48	39	55
85	45	19	52
90	43	0	49
95	39	0	42
99	34	0	<1

[a] After non-selective hydrolysis of the ester product from a single step kinetic resolution.

Table 1 : Comparison of overall theoretical yields of alcohol obtainable using this double kinetic resolution strategy (E = 15 for each step), Scheme 1, with those obtainable by conventional methods.

As can be seen from Table 1, this double kinetic resolution strategy results in an improvement in overall product yield for a range of enantiomeric excesses. However, since the product rather than the starting material is required from each kinetic resolution used in this double kinetic resolution strategy there is still a limit to the maximum enantiomeric excess achievable.

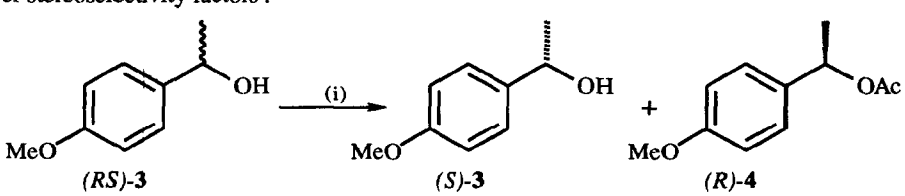
It should be noted that the only difference between the present strategy and the conventional one step esterification followed by hydrolysis of the kinetically resolved ester product is the use of the lipase in the second as well as in the first step. Therefore the theoretical benefits of the proposed strategy should be realisable in practice.

Calculations as shown in Table 2 using the computer model indicated that, for a final product enantiomeric excess of 95% (when E = 15 for both kinetic resolutions), maximum yield using the double kinetic resolution strategy described above would be obtained by allowing the first kinetic resolution to run to 52% conversion and the second kinetic resolution to run to 81% conversion.

Conversion (%) in first kinetic resolution.	ee (%) of product from first kinetic resolution.	Conversion (%) in second kinetic resolution to give a product with 95% ee.	Overall yield.(%)
45	77.5	88	39.6
48	75.8	85	40.8
49	75.1	84	41.2
50	74.4	83	41.5
51	73.7	82	41.8
52	72.8	81	42.1
53	71.9	79	41.9
54	71.0	77	41.6
55	69.9	75	41.3

Table 2 : Calculation of the % conversion required (in each kinetic resolution) to give the maximum possible overall yield of product with 95% ee using this double kinetic resolution strategy.

The alcohol 1-(4-methoxyphenyl)ethanol **3** was chosen as a suitable substrate on which to demonstrate this double kinetic resolution strategy on the basis of work performed by Schneider *et al.*[4] In order to find the most suitable lipase, kinetic resolutions of *(RS)*-**3** and of the corresponding acetate *(RS)*-**4** were performed with a number of common lipases: *Pseudomonas fluorescens* lipase (PFL); Pig pancreatic lipase (PPL) and *Candida cylindracea* lipase (CCL). Esterification of *(RS)*-**3** in dichloromethane using vinyl acetate as the acyl donor proceeded as shown in Scheme 2. With each of the lipases used, the *R* enantiomer of **3** was found to be the faster reacting. With PFL the kinetic resolution of *(RS)*-**3** proceeded with a stereoselectivity factor of approximately 15 while esterifications of *(RS)*-**3** with PPL and CCL were found to proceed very slowly and with lower stereoselectivity factors .



(RS)-**3** *(S)*-**3** *(R)*-**4**

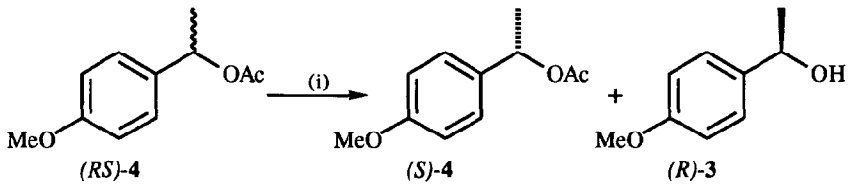
(i) Lipase, vinyl acetate, CH_2Cl_2.

Lipase	% Conversion[a]	% ee Recovered reactant (**3**)[b]	% ee Product (**4**)[c]	E_R[d]	E_P[d]
PFL	44	61	77	14.7	14.1
PPL	30	21	/	3.6	/
CCL	20	10	/	2.6	/

[a] Measured by ^1H NMR spectroscopy of the crude product. [b] Measured by use of the chiral shift reagent:(+)-Eu(hfc)$_3$ followed by ^1H NMR spectroscopy or by preparation of Mosher's ester derivatives[5] followed by ^1H or ^{19}F NMR spectroscopy. [c] Measured as described for **3** after hydrolysis (K_2CO_3/MeOH). [d] E_R and E_P are the stereoselectivity factors calculated using the standard formulae[3] with respect to the reactant and product respectively.

Scheme 2 : Enzymic esterification of 1-(4-methoxyphenyl)ethanol **3**.

Enzymic hydrolysis (pH 7) of *(RS)*-1-(4-methoxyphenyl)ethyl acetate **4** proceeded as shown in Scheme 3. Since in the esterification reactions (Scheme 2) the *R* enantiomer of **3** was found to be the faster reacting enantiomer, it was expected that in the reverse (hydrolysis) reactions the *R* enantiomer would again be the faster reacting. As shown in Scheme 3 this was indeed found to be the case. As with the acetylation of **3**, PFL was found to be the most selective of the three lipases tried in the hydrolysis proceeding with a similar stereoselectivity factor of approximately E = 15.



(RS)-**4** *(S)*-**4** *(R)*-**3**

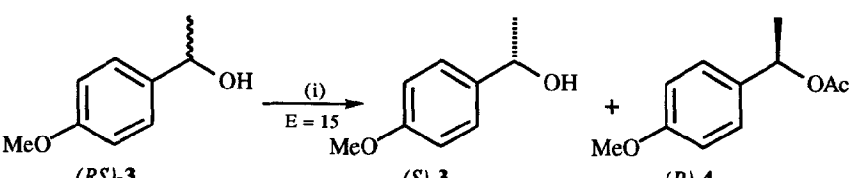
(i) Lipase, pH 7 buffer.

Lipase	Conversion (%)[a]	ee (%) Recovered reactant (**4**)[b]	ee (%) Product (**3**)[c]	E_R[d]	E_p[d]
PFL	51	77	73	15.3	14.4
PPL	61	28	32	1.8	3.1
CCL	40	8	30	1.4	2.2

[a] Measured by ^{1}H NMR spectroscopy of the crude product. [b] Measured as described for **3** after hydrolysis (K_2CO_3/MeOH). [c] Measured by use of the chiral shift reagent: (+)-Eu(hfc)$_3$ followed by ^{1}H NMR spectroscopy or by preparation of Mosher's ester derivatives[5] followed by ^{1}H or ^{19}F NMR spectroscopy. [d] Calculated using the standard formulae.[3]

Scheme 3 : Enzymic hydrolysis of 1-(4-methoxyphenyl)ethyl acetate **4**.

Having established the stereoselectivity factors for the forward and reverse reactions the double kinetic resolution was performed on *(RS)*-1-(4-methoxyphenyl)ethanol **3** using PFL with the aim of obtaining each enantiomer with an ee >95%. In the first kinetic resolution, the PFL mediated acetylation, (Scheme 4) the conversion was monitored by ^{1}H NMR spectroscopy. The reaction was stopped at 51% conversion close to the optimal value (Table 2). Work-up and flash chromatography enabled isolation of the recovered substrate *(S)*-**3** in 47% yield and the ester product *(R)*-**4** in 48% yield. The enantiomeric excess of the recovered alcohol **3** was measured by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent: (+)-Eu(hfc)3. The enantiomeric excess of the product **4** was measured by the same technique after chemical hydrolysis (potassium carbonate/methanol). The acetate **4** had an enantiomeric excess of 74% and the recovered alcohol **3** had an enantiomeric excess of 76%.

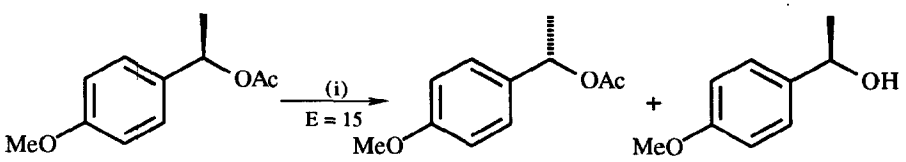


(RS)-**3** *(S)*-**3** 76% ee 47% yield *(R)*-**4** 74% ee 48% yield

(i) PFL, vinyl acetate, CH_2Cl_2. 51% conversion.

Scheme 4 : First kinetic resolution.

The acetate *(R)*-**4** (74% ee) from the first kinetic resolution was used as the starting material in the second kinetic resolution in which the PFL mediated hydrolysis was performed (Scheme 5). The extent of the reaction was followed by monitoring the amount of 1M sodium hydroxide dispensed by the autotitrator in order to maintain the reaction mixture at pH 7. At the appropriate conversion (82%, Table 2) the reaction was halted. Work-up followed by flash chromatography gave recovered acetate *(S)*-**4** in 12% yield with an enantiomeric excess of 27% and the alcohol *(R)*-**3** in 77% yield with an enantiomeric excess of >95%.



(R)-**4**
74% ee

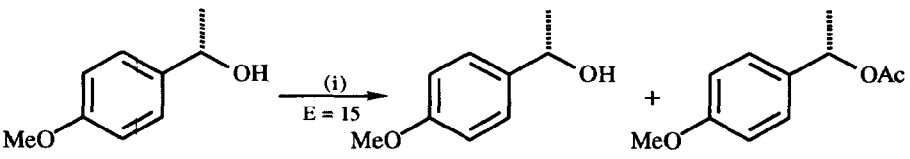
(S)-**4**
27% ee
12% yield

(R)-**3**
>95% ee
77% yield

(i) PFL, pH 7 buffer. 82% conversion.

Scheme 5 : Second kinetic resolution.

For completeness, the recovered reactant *(S)*-**3** (76% ee) from the first kinetic resolution was treated again with PFL and vinyl acetate in dichloromethane, the reaction being stopped after 20% conversion. After work-up and flash chromatography, *(S)*-**3** was obtained with an enantiomeric excess of >95% and a yield of 70% (Scheme 6).



(S)-**3**
76% ee

(S)-**3**
>95% ee
70% yield

(S)-**4**
7% ee
15% yield

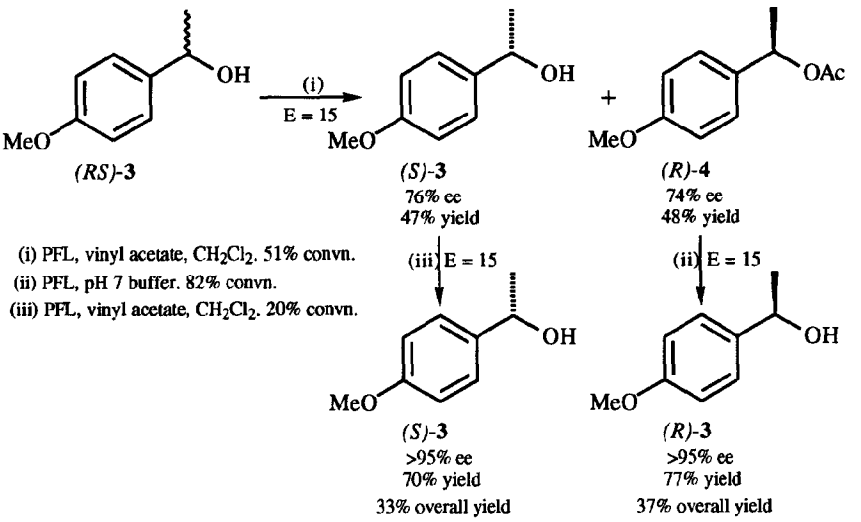
(i) PFL, vinyl acetate, CH_2Cl_2. 20% convn.

Scheme 6 : Preparation of *(S)*-**3** (>95% ee) by treating the recovered reactant from the first kinetic resolution with PFL and vinyl acetate in dichloromethane.

Conclusion:

The ability of lipase to catalyse both esterifications and saponifications allows the faster reacting enantiomer of alcohol substrates to be obtained in high ee and good yield by a double kinetic resolution strategy involving sequential catalysis of acetylation and hydrolysis. Application of the strategy to 1-(4-methoxyphenyl)ethanol **3** allowed this racemic substrate to be resolved with both enantiomers being obtained in >95% ee, the faster reacting in 37% overall yield and the slower in 33% yield (Scheme 7).

In cases where lipases are available that allow a choice of the faster reacting enantiomer the double kinetic resolution may be used to advantage over the conventional one step process for maximisation of the yield of a particular enantiomer with relatively little compromise being required in terms of the enantiomeric excess.



Scheme 7 : Overall strategy for the resolution of 1-(4-methoxyphenyl)ethanol

Experimental:

^{1}H nmr spectra were recorded on a Bruker WH300 spectrometer at 300 MHz in $CDCl_3$ and referenced to residual protio solvent. ^{19}F nmr spectra were recorded on a Bruker AM250 spectrometer at 235.35 MHz in $CDCl_3$. Optical rotations were measured at 22°C using a Perkin-Elmer 241 polarimeter. PFL was obtained from Fluka while PPL and CCL were from Sigma.

Preparation of 1-(4-methoxyphenyl)ethanol **3**

4-Methoxyacetophenone (15.0 g, 0.10 mol) in Et_2O (100 mL) was added slowly to a mixture of $LiAlH_4$ (5.0 g, 0.13 mol) in Et_2O (200 mL) at 0°C under a nitrogen atmosphere. After stirring for 3 h at 0°C and then 3 h at room temperature, TLC indicated that all of the starting material had been consumed. The reaction mixture was cooled to 0°C and the excess $LiAlH_4$ was carefully quenched with 5 : 1 Et_2O:water (25 mL), 15% w/v NaOH solution (5 mL) and water (15 mL). The insoluble inorganic salts were removed by filtration through celite. Concentration of the filtrate *in vacuo* yielded the required product **3** (14.3 g, 94%). δ_H 7.32 [2H, d, J 8.6 Hz, Ph (*meta* to OMe)], 6.90 [2H, d, J 8.6 Hz, Ph (*ortho* to OMe)], 4.87 [1H, q, J 6.6 Hz, CHOH], 3.82 [3H, s, OCH_3], 1.82 [1H, br s, OH], 1.50 [3H, d, J 6.6 Hz, CH_3].[6]

Preparation of 1-(4-methoxyphenyl)ethyl acetate **4**[7]

To a stirred solution of **3** (2.00 g, 13.2 mmol), triethylamine (1.59 g, 15.6 mmol) and 4-(dimethylamino)pyridine (5 mg) in CH_2Cl_2 (50 mL) was added acetic anhydride (1.46 g, 14.3 mmol). After stirring for 6 h at room temperature, TLC indicated that all of the starting material had been consumed. The reaction mixture was washed with saturated $NaHCO_3$ solution (30 mL) and after drying ($MgSO_4$), the organic layer was concentrated *in vacuo*. Flash chromatography (silica, 1 : 1, Et_2O : petrol) gave the required product **4** (2.23 g, 87%): δ_H 7.32 [2H, d, J 8.7 Hz, Ph (*meta* to OMe)], 6.90 [2H, d, J 8.7 Hz, Ph (*ortho* to OMe)], 5.85 [1H, q, J 6.6 Hz, CHOAc], 3.82 [3H, s, OCH_3], 2.07 [3H, s, $OCOCH_3$], 1.54 [3H, d, J 6.6 Hz, CH_3].

Measurement of the enantiomeric excesses of **3** *and* **4**.

For the alcohol **3**, preparation of Mosher's ester derivatives[5] as described below followed by ^1H and ^{19}F NMR spectroscopy enabled enantiomeric excess measurement. A solution of (R)-(+)-α-methoxy-α-(trifluormethyl)phenylacetic acid (23 mg, 0.1 mmol) in toluene (2 ml) was treated with oxalyl chloride (16 μL, 0.2 mmol) and dimethylformamide (0.05 mL). The reaction mixture was stirred at room temperature for 30 min. Solvent and excess oxalyl chloride were then removed in vacuo to give the acid chloride. Dichloromethane (5 mL) was added and the solution used immediately. The alcohol **3** (0.1 mmol) in dichloromethane (5 mL) was treated with 4-(dimethylamino)pyridine (5 mg), triethylamine (66 μL, 0.2 mmol) and the solution of the acid chloride. The reaction was monitored by TLC. When all the alcohol had been consumed, N,N-dimethylamonoethanol (0.1 mL) was added and the solvent removed in vacuo. The residue was dissolved in 1 : 4 Et_2O : petrol and filtered through an alumina (grade V) plug. Removal of the solvent gave the Mosher's ester as a colourless oil. In the ^1H NMR spectrum of the Mosher's ester derivative of **3**, signals for the methoxy group were observed at ~ 3.55 ppm [*(S)*-**3**] and at ~ 3.47 ppm [*(R)*-**3**]. In the ^{19}F NMR spectrum, signals were observed at ~ -73.3 ppm [*(R)*-**3**] and at ~ -73.6 ppm [*(S)*-**3**]. Alternatively ^1H NMR spectroscopy of **3** in the presence of 1.5 equivalents of the chiral shift reagent *tris*-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) [(+)-Eu(hfc)$_3$] gave rise to signals for the methyl group at ~ 9.4 ppm [*(S)*-**3**] and ~ 9.3 ppm [*(R)*-**3**].[8] The enantiomeric excess of the ester **4** was measured as described above after chemical hydrolysis (K_2CO_3/MeOH) to **3**.

PFL mediated esterification of racemic 1-(4-methoxyphenyl)ethanol **3**: *first step of double kinetic resolution.*

To a stirred solution of **3** (2.48 g, 16.3 mmol) and vinyl acetate (2.77 g, 32.2 mmol) in CH_2Cl_2 (30 mL) was added PFL (40 mg). The reactants were stirred at room temperature for 18 d, extent of reaction was monitored by ^1H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 51%. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and gave recovered starting material [*(S)*-**3**] (1.173 g, 47%) {$[\alpha]_D^{22}$ = -44.5 (c = 1.0, $CHCl_3$), literature [*(R)*-**3**: 85% ee][9]: $[\alpha]_D^{20}$ = +44.2 (c = 0.9 - 1.1, $CHCl_3$)} and the required product [*(R)*-**4**] (1.53 g, 48%) {$[\alpha]_D^{22}$ = +89.8 (c = 0.9, $CHCl_3$)}. Enantiomeric excesses were measured as described above, **3** was obtained with an enantiomeric excess of 76%, and **4** was obtained with an enantiomeric excess of 74%. The product **4** and the recovered reactant **3** were used as starting materials in second kinetic resolutions as described below.

PFL mediated hydrolysis of scalemic 1-(4-methoxyphenyl)ethyl acetate **4**: *second step of double kinetic resolution.*

PFL (30 mg) was added to a stirred mixture of *(R)*-1-(4-methoxyphenyl)ethyl acetate **4** (74% ee) (0.50 g, 2.6 mmol) in pH 7 phosphate buffer (10 mL). As the reaction proceeded the pH was maintained by use of an autotitrator dispensing 1M NaOH solution. When 2.12 mL of NaOH solution had been added (corresponding to 82% conversion) the reaction was stopped by extraction with CH_2Cl_2 (10 x 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was removed *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 82%. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and gave recovered starting material [*(S)*-**4**] (0.060 g, 12%) {$[\alpha]_D^{22}$ = -32.7 (c = 1.0, $CHCl_3$)} and the required product [*(R)*-**3**] (0.302 g, 77%) {$[\alpha]_D^{22}$ = +58.6 (c = 1.0, $CHCl_3$)}. Enantiomeric excesses were measured as described above, **4** was obtained with an enantiomeric excess of 27%, and **3** was obtained with an enantiomeric excess of >95%.

PFL mediated esterification of scalemic 1-(4-methoxyphenyl)ethanol **3**: *continuation of the first step of the double kinetic resolution.*

To a stirred solution of *(S)*-**3** (76% ee) (0.50 g, 3.3 mmol) and vinyl acetate (0.57 g, 6.6 mmol) in CH_2Cl_2 (30 mL) was added PFL (50 mg). The reactants were stirred at room temperature for 26 d, extent of reaction was monitored by ^1H NMR spectroscopy. Filtration of the reaction mixture to remove the enzyme was followed by removal of solvent and excess vinyl acetate *in vacuo*. ^1H NMR spectroscopy of the crude product indicated a conversion of 20%. Flash chromatography was performed (silica, 1 : 1, Et_2O : petrol) and gave recovered starting material [*(S)*-**3**] (0.348 g, 70%) {$[\alpha]_D^{22}$ = -55.7 (c = 1.2, $CHCl_3$)} and product [*(S)*-**4**] (0.093 g, 15%) {$[\alpha]_D^{22}$ = -8.5 (c = 1.2, $CHCl_3$)}. Enantiomeric excesses were measured as described above, **3** was obtained with an enantiomeric excess of >95%, and **4** was obtained with an enantiomeric excess of 7%.

Computer model used to predict the outcome of kinetic resolutions. †
The programme was written on an Apple Macintosh Computer using Microsoft Basic. Listing:

```
10 INPUT "% Enantiomeric excess of starting material =";SM
20 IF SM>100 GOTO 360
30 IF SM<-100 GOTO 360
40 INPUT "Stereoselectivity factor =";E
50 IF E=0 GOTO 360
60 INPUT "Number of points to be displayed =";D
70 EE=SM/100
80 A=1/(D-1)
90 RP=0
100 SP=0
110 B=0
120 RSM=((1 +EE)/2)
130 SSM=(1-RSM)
140 PRINT " %convn %eeSM %eeprod"
150 FOR Z=.001 TO .999 STEP .001
160 N=((E*RSM)+(SSM))
170 RPF=((.001*(RSM*E))/N)
180 SPF=((.001*SSM)/N)
190 RSM=RSM-RPF
200 SSM=SSM-SPF
210 RP=RP+RPF
220 SP=SP+SPF
230 C=100*Z
240 IF Z=.999 GOTO 260
250 IF Z>=B GOTO 260 ELSE 300
260 B=B+A
270 EESM=(100*((RSM-SSM)/(RSM+SSM)))
280 EEP=(100*((RP-SP)/(RP+SP)))
290 PRINT USING "####.##";C,EESM,EEP
300 NEXT Z
310 PRINT "Initial % ee of starting material =";SM
320 PRINT "Stereoselectivity factor=";E
330 FOR JdS = 1 TO 10000
340 NEXT JdS
350 END
360 PRINT "Invalid value - programme stopped"
370 FOR JdS = 1 TO 10000
380 NEXT JdS
390 END
```

Example of Input:

```
% Enantiomeric excess of starting material =? 50
Stereoselectivity factor =? 10
Number of points to be displayed =? 11
```

Example of Output:*

%convn	%eeSM	%eeprod
0.10	49.96	93.55
10.00	45.20	93.16
20.00	39.33	92.69
30.00	31.95	92.12
40.00	22.41	91.39
50.00	9.57	90.43
60.00	-8.57	89.04
70.00	-35.79	86.77
80.00	-76.82	81.71
90.00	-99.87	66.65
99.90	-100.00	50.15

Initial % ee of starting material = 50
Stereoselectivity factor= 10

*Negative enantiomeric excesses indicate that the material is enriched in the opposite enantiomer.

† This programme gives satisfactory results in straightforward cases as described above, however for general applications a programme such as FACSIMILE (AEA Technology, Harwell, UK) is recommended.

Acknowledgements:

We thank the SERC and ICI Fine Chemicals Manufacturing Organisation for a CASE award (to J.A.A. de S.).

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