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PPL-CATALYZED RESOLUTION OF 1,2- AND 1,3-DIOLS IN METHYL PROPIONATE AS SOLVENT AN APPLICATION OF THE TANDEM USE OF ENZYMES.

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Abstract The Porcine Pancreatic Lipase (PPL)-catalyzed transesterification of 1-phenyl-1,2-ethanediol **1**, *2-phenyl-1,2-propanediol* **2**, *1,2-decanediol* **3**, *1,2-pentanediol* **4**, *1,2-butanediol* **5**, *1,2-propanediol* **6** *and 1,3-butanediol* **7** *in methyl propionate as solvent was evaluated In all substrates, the primary hydroxy group is esterified exclusively The enantioselectivity displayed in this PPL-catalyzed reaction is moderate The enantiomeric excess of diol* (−)-**1** *is enhanced by subjecting propionate* (−)-**8**, *with a moderate ee (obtained by a PPL-catalyzed esterification of racemic* **1** *in methyl propionate), to an enzyme-catalyzed hydrolysis (tandem principle)*

Introduction

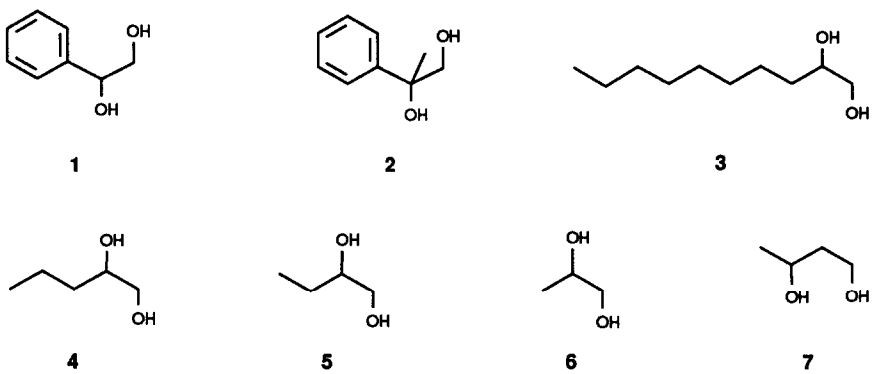
The utility of enzymes for regio- and/or enantioselective esterification of alcohols in organic media is well documented in the literature[1] It is generally known[2-10], that the enzyme-catalyzed esterification of primary alcohols takes place at a much higher rate than that of secondary alcohols This feature is of special importance for the regioselective acylation of the primary hydroxy group of 1,2- and 1,3-diols, because conventional methods[8] always produce a mixture of primary and secondary esters, which are usually difficult to separate Moreover, conventional methods often give a considerable amount of diacylated product In addition to the regioselective behavior, enzymes also may be able to discriminate between enantiomeric diols, which conventional methods cannot

In 1984, Cambou and Klibanov[7] reported the esterification of 1,2-butanediol catalyzed by Candida Cylindracea Yeast Lipase (CCL) in a biphasic system which consisted of a phosphate buffer (pH 8 0) and tributyrin as the matrix ester In this system, the primary alcohol is esterified with a high degree of regio- and enantioselectivity Recently, Oehlschlager *et al*[9] found that the acylation of some alifatic di- and triols, catalyzed by PPL in ether or tetrahydrofuran as the reaction medium and using acetic- or butyric anhydride as the acyl donor, takes predominantly place at the primary alcohol It was also reported, that some enantioselectivity is observed when the PPL-catalyzed esterification of 1,3-butanediol, employing trifluoroethyl butyrate as the acylating agent, proceeds past monoacylation In 1985, Klibanov *et al*[8] described the PPL-catalyzed transesterification of a series of 1,2- and 1,3-diols in organic solvents, such as ethyl acetate, propionate or butyrate, which serve as acylating agent as well With these solvent-ester combinations the primary alcohol is esterified exclusively However, it is of importance to note that the enantioselectivity of these reactions has not been investigated The enzyme-catalyzed esterification of 1,2- and 1,3-diols, using alkyl carboxylates as

reaction medium has barely been investigated ever since The only other example[10] of regioselective lipase-catalyzed esterification of a 1,3-diol in an alkyl carboxylate as solvent, is the Chromobacterium Viscosum-catalyzed esterification of enantiopure chloramphenicol in methyl acetate

In a recent paper[11], we reported the PPL-catalyzed resolution of a series of primary and secondary alcohols in methyl propionate as solvent It was found, that chiral primary alcohols are esterified rapidly, albeit with a low enantioselectivity, while chiral secondary alcohols are esterified at a low rate, but in a highly enantioselective manner These results were a stimulus to investigate the catalytic activity of PPL toward chiral diols in an organic medium which serves as acylating agent as well The chiral diols studied contain besides a primary hydroxy group either a secondary or tertiary alcohol function at the stereogenic center, so both the regio- and enantioselectivity of the transesterification reaction can be evaluated For this purpose, a series of 1,2-diols, *viz* **1** - **6**, and a 1,3-diol, *viz* **7** (Chart 1), were selected and subjected to a PPL-catalyzed esterification in methyl propionate The results of these enzymatic transesterifications will be presented in this paper

Chart 1



PPL-catalyzed resolution of diols 1 - 7

First, the PPL-catalyzed resolution of 1-phenyl-1,2-ethanediol **1** was studied in methyl propionate as solvent at 40°C in the presence of molecular sieves 4Å (Scheme 1) After incubation for 4 h, a GLC-analysis revealed that the reaction mixture consisted of monoester and remaining diol only No diester could be detected After separation of monoester and diol, a 400 MHz ^{1}H-NMR-analysis of the former showed that only esterification of the primary alcohol function had occurred to give propionate (–)-**8** This propionate was then hydrolyzed[12] with sodium hydroxide in ethanol to give diol (–)-**1** The same procedure as described for diol **1** was applied to diols **2** - **7** The results of these reactions are collected in Table 1 Without exception the propionate of the primary alcohol was formed exclusively Less than 1% of diester is present, as was determined by capillary GLC These results show the excellent regioselectivity displayed by the biocatalyst PPL The enantioselectivity of these transesterification reactions, however, was disappointingly low, as indicated by the enantiomeric ratios E With regard to the stereochemistry, for all substrates the enantiomer having the (*R*)-configuration was esterified preferentially by PPL The rate of esterification increased in the change from

aromatic diols **1** and **2** to diol **6**. 1,3-Butanediol **7** was transesterified at an even higher rate than the 1,2-diols

Scheme 1

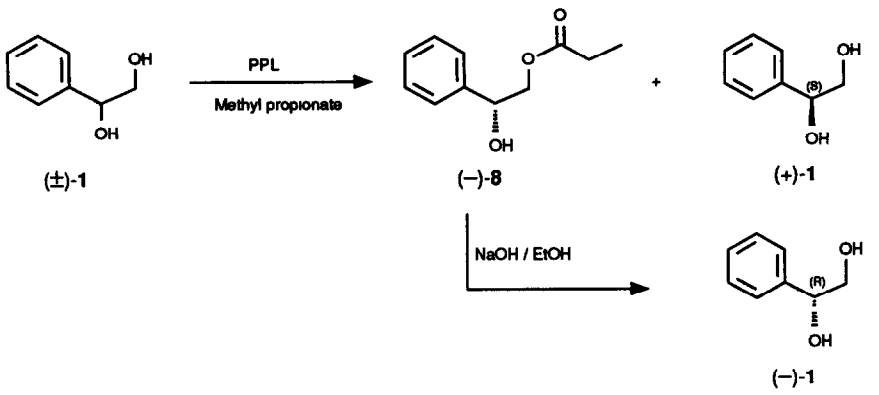


Table 1 PPL-catalyzed transesterification of 1,2- and 1,3-diols in methyl propionate [a]

substr	monoester[b,c]		diol	conv [f]	E[g]
	ee_p[d,e]	config [e]	ee_s[d,e]		
1	36	*R*	25	41	2 7
2	24	*R*	18	43	1 9
3	16	*R*	21	58	1.7
4	11	*R*	30	72	1 6
5	9	*R*	26	74	1 5
6	10	*R*	23	69	1 5
7	8	*R*	59	88	1 8

a. reaction conditions 4 0 mmol of substrate, 20 ml of methyl propionate 800 mg of PPL, 400 mg of molecular sieves 4Å, 40°C, 4 h For details see the experimental section.

b less than 1% of diester is present, as was determined by capillary GLC

c no secondary ester is present, as was determined by 90 or 400 MHz ^{1}H-NMR (see the experimental section)

d enantiomeric excess (in %) of the diol obtained by hydrolysis of the enzymatically produced monoester (ee_p) or of the recovered diol (ee_s)

e determined by comparison of the optical rotation with literature data (see the experimental section)

f conversion (in %) calculated according to the formula conv = ee_s / (ee_s + ee_p) (ref 13)

g enantiomeric ratio calculated according to the formula $E = \ln(1 - conv(1 + ee_p)) / \ln(1 - conv(1 - ee_p))$ (ref 13)

Structural evidence for the formation of a primary propionate is given for 1,2-decanediol monopropionate (Figure 1) According to the Strehlow incremention rules[14], for H_1 a δ-value of 4 16 ppm and for H_2 a

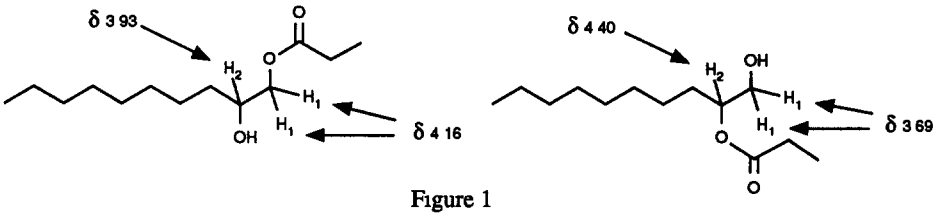


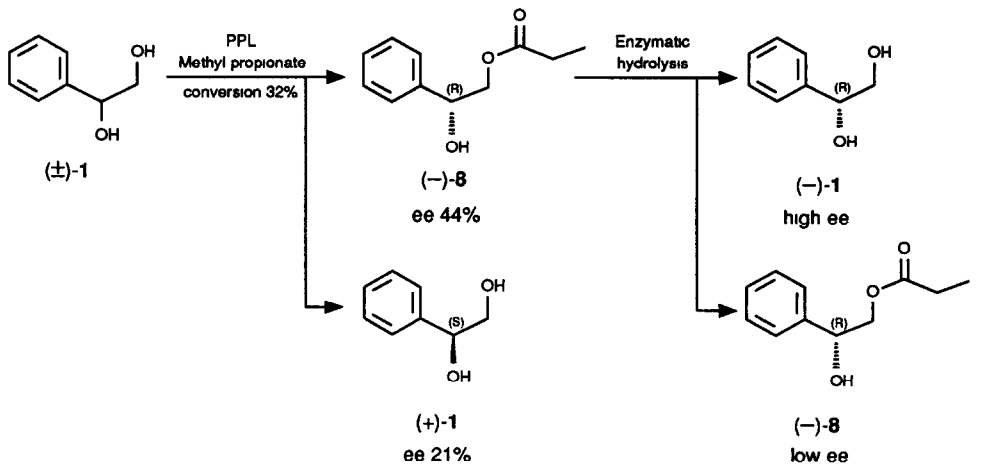
Figure 1

δ-value of 3 93 ppm is calculated. In the actual ^{1}H-NMR spectrum these protons are positioned at δ 4 05 and δ 3 83 ppm, respectively, which is in good agreement with the calculated chemical shifts Similar calculations performed for the secondary propionate, show that H_1 should be positioned at δ 3 69 ppm and H_2 at δ 4 40 ppm, which contradicts the experimental δ-values

Tandem use of enzymes

It is known in the literature[15-21], that the enantiomeric preference of enzymes displayed under non-aqueous conditions is not altered under hydrolytic conditions When the esterification of a certain enantiomer of an alcohol is preferentially catalyzed by an enzyme in organic media, then the hydrolysis of the ester of the same enantiomer will be preferentially catalyzed in aqueous media This principle provides a tool to enhance the enantiomeric purity of the (*R*)-enantiomer of diol **1**, *viz* by subjecting the optically enriched propionate (−)-**8** to a subsequent enzyme-catalyzed hydrolysis (Scheme 2) For this purpose, three biocatalysts were

Scheme 2



considered as the tandem enzyme, *viz* PPL, Mucor Esterase and Pig Liver Esterase (PLE) Optically enriched (−)-**8** (ee 44%) was obtained by a PPL-catalyzed resolution of diol **1** in methyl propionate at room temperature The results of the subsequent enzymatic hydrolyses are collected in Table 2 This table shows that at pH 7 0 a rapid hydrolysis of the ester is attained with all enzymes Especially with Mucor Esterase as the catalyst (entry 1), the enantiomeric excess of the diol (−)-**1** (ee_p) increased considerably The hydrolysis of

propionate (−)-**8** catalyzed by Mucor Esterase at pH 9.0[#] (entry 2) took place at a much lower rate and did not give an improvement of the enantiomeric purity of diol (−)-**1**, as compared with the hydrolysis at pH 7 0 From these results it may be concluded, that the ee of diol (−)-**1** can be enhanced by a tandem use of enzymes

Table 2: Enzymatic hydrolysis of optically enriched 2-hydroxy-2-phenyl-1-ethyl propanoate (ee 44%) [a]

				diol			remaining ester			
entry	enzyme (amounts)	pH	time, min.	$[\alpha]^{25}_D$ [b]	ee_p [c,d]	config.[d]	$[\alpha]^{25}_D$ [b]	ee_s [c,d]	config [d]	conv [e]
1	Mucor (100mg)	7 0	70	−29 0 (c 2 51)	73	*R*	−4.1 (c 2 75)	10	*R*	54
2	Mucor (100mg)	9 0	250	−28.7 (c 1 85)	72	*R*	−10 5 (c 3 04)	27	*R*	38
3	PPL (200mg)	7 0	80	−24 7 (c 3 13)	62	*R*	−10 3 (c 2 92)	26	*R*	50
4	PLE (200µl)	7 0	25	−25 2 (c 2 11)	64	*R*	−7 2 (c 3 05)	18	*R*	57

a reaction conditions 2 0 mmol of substrate with starting enantiomeric excess (ee_0) 44%, (*R*)-configuration, 40 ml of 0 05 M phosphate buffer, room temperature For details see the experimental section

b optical rotation (in degrees) in ethanol

c enantiomeric excess (in %) of the diol (ee_p) or of the diol obtained by hydrolysis of the recovered monoester (ee_s)

d determined by comparison of the optical rotation with the literature for (*R*), $[\alpha]^{25}_D$ −39 6° (c 2.44, ethanol), for (*S*), $[\alpha]^{25}_D$ +39 3° (c 3 13, ethanol) (ref 22)

e conversion (in %) calculated according to the formula conv = ((−ee_s) + ee_0) / ((−ee_s) + ee_p)(ref 13 and 23)

The results presented in this paper clearly show that PPL is a very efficient catalyst for the regioselective esterification of the primary alcohol function of 1,2- and 1,3-diols in methyl propionate as solvent Although the enantioselectivity displayed by the biocatalyst in these reactions is moderate, the antipode that is preferentially esterified can be obtained with satisfactory enantiomeric purity by a tandem use of enzymes, *i e* by subjecting the enzymatically produced monoester to a subsequent enzyme-catalyzed hydrolysis

Experimental section

General remarks

^{1}H-NMR spectra were recorded on a Bruker WH-90 (90 MHz) or a Bruker AM-400 (400 MHz) spectrometer with TMS as the internal standard GLC-analyses were performed using a HP 5790A or a HP 5890, containing a cross-linked methyl silicone column (25 m) Column chromatography was performed using Merck Kieselgel 60 F254 For the determination of optical rotations a Perkin Elmer 241 Polarimeter was used Porcine Pancreatic Lipase (PPL) and Pig Liver Esterase (PLE) were purchased from Sigma Mucor Esterase was obtained as a gift from Gist-brocades, Delft, The Netherlands PPL was dried at reduced pressure (~0 02 mbar) during 4h prior to use The solvents used for the enzymatic resolutions were stored on molecular sieves 4Å (10% w/v) All glassware was oven dried before use Substrates **1** - **7** were either in stock or purchased from Janssen Chimica

[#] In a later stage of our studies we found that the enantioselectivity of the Mucor Esterase-catalyzed resolution of diol **1** in methyl propionate was slightly improved using enzyme precipitated at a higher pH-value The rate of this reaction, however, was low

PPL-catalyzed transesterification of 1-phenyl-1,2-ethanediol, (±)-1, general procedure.

PPL (800 mg) and molecular sieves 4Å (400 mg) were added to a solution of (±)-1 (0.56 g; 4.0 mmol) in methyl propionate (20 ml). The suspension was stirred at 40°C for 4 h, then the solids were filtered off and washed with ether (3x10 ml) GLC-analysis of the filtrate showed the presence of starting material and of monoester. No diester could be detected. After evaporation of the solvents, the monoester and remaining diol were separated by column chromatography (silicagel / pet ether 60-80°C - ethyl acetate (2.1) → (1·2)), giving 0 32 g (57%) diol and 0 32 g (41%) monoester. The optical purity of the monoester was determined after alkaline hydrolysis according to the procedure of Cesti *et al* [12]. the monopropionate (0.32 g; 1.6 mmol) was stirred overnight in a 1 M solution of sodium hydroxide in ethanol (5 ml) at room temperature. After evaporation of the ethanol, the residue was taken up in water (5 ml) and extracted with ether (4x5 ml). The combined extracts were dried on $MgSO_4$ and concentrated. The residue was chromatographed (silicagel / pet ether 60 - 80°C - ethyl acetate (2:1) → (1·2)) affording chemically pure diol

The PPL-catalyzed resolution of 1,2-diols **2** - **6** and 1,3-diol **7** was carried out in the same manner as described for (±)-**1** The relevant data of these reactions are collected in Table 1. ^{1}H-NMR-spectra of the monoesters, optical rotations as well as literature data are given below

1-Phenyl-1,2-ethanediol (1)

Resolution: diol obtained by alkaline hydrolysis of the propionate, $[\alpha]^{25}_D$ −14.5° (c 2.1, H_2O), ee 36%, (*R*)-configuration; recovered diol, $[\alpha]^{25}_D$ +10 1° (c 2.9, H_2O), ee 25%, (*S*)-configuration (lit.[24] for (*R*), $[\alpha]^{24}_D$ −40 5° (c 2 8, H_2O), ee 100%, for (*S*), $[\alpha]^{24}_D$ +40.7° (c 3.3, H_2O), ee 100%).

Monoester: ^{1}H-NMR ($CDCl_3$,400 MHz) δ 1 15 (3H, t, J = 7 6 Hz; -CH_3), 2 38 (2H, q, J = 7.6 Hz, -CH_2CH_3), 2 60 (1H, s(br), -OH), 4 17 (1H, dd, J = 8.4 and 12 6 Hz, -CH_2O-), 4 29 (1H, dd, J = 3.3 and 12 6 Hz, -CH_2O-), 4 96 (1H, dd, J = 3 3 and 8 3 Hz, -CH(OH)-), 7 31 - 7 41 (5H, m, 5ArH)

2-Phenyl-1,2-propanediol (2)

Resolution· diol obtained by alkaline hydrolysis of the propionate, $[\alpha]^{25}_D$ −2.2° (c 3.7, ether), ee 24%, (*R*)-configuration; recovered diol, $[\alpha]^{25}_D$ +1 6° (c 4 2, ether), ee 18%, (*S*)-configuration (lit.[25] for (*S*), $[\alpha]^{22}_D$ +8 99° (c 5 8, ether), ee 100%)

Monoester: ^{1}H-NMR ($CDCl_3$, 90 MHz) δ. 1 09 (3H, t, J = 7 0 Hz; -CH_2CH_3), 1.57 (3H, s; -CH_3), 2 33 (2H, q, J = 7 0 Hz, -CH_2CH_3), 2 63 (1H, s; -OH), 4 20 (1H, d, J = 11 Hz, -CH_2O-), 4 34 (1H, d, J = 11 Hz; -CH_2O-), 7 24 - 7 53 (5H, m; 5ArH)

1,2-Decanediol (3)

Resolution: diol obtained by alkaline hydrolysis of the propionate, $[\alpha]^{25}_D$ +1 9° (c 0 5, methanol), ee 16%, (*R*)-configuration, recovered diol, $[\alpha]^{25}_D$ −2.6° (c 0.5, methanol), ee 21%, (*S*)-configuration (lit[26] for (*S*), $[\alpha]^{22}_D$ −11.9° (c 0.43, methanol), ee not clearly indicated but between 94 and 100%.

Monoester ^{1}H-NMR ($CDCl_3$, 400 MHz) δ· 0.88 (3H, t, J = 6.8 Hz, -CH_3), 1.16 (3H, t, J = 7 6 Hz, -$COCH_2CH_3$), 1.27 - 1.36 (11H, m, alifatic chain), 1.44 - 1 49 (3H, m, alifatic chain), 2.02 (1H, s(br), -OH), 2 38 (2H, q, J = 7.6 Hz, -$COCH_2CH_3$), 3.83 (1H, m; -CH(OH)-), 3 96 (1H, dd, J = 7 3 and 11 4 Hz, -CH_2O-), 4 15 (1H, dd, J = 3 0 and 11 4 Hz, -CH_2O-)

1,2-Pentanediol (4)

Resolution. diol obtained by alkaline hydrolysis of the propionate, $[\alpha]^{25}_D$ +1 9° (c 2 4, ethanol), ee 11%, (*R*)-configuration, recovered diol, $[\alpha]^{25}_D$ −4.8° (c 1 6, ethanol), ee 30%, (*S*)-configuration (lit.[27] for (*S*), $[\alpha]^{25}_D$ −16 1° (c 3, ethanol), ee 100%, lit [28] for (*R*), $[\alpha]_D$ +16 2° (c 14, ethanol).

Monoester. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0 94 (3H, t, J = 3 5 Hz, -CH_3), 1 16 (3H, t, J = 7 6 Hz, -$COCH_2CH_3$), 1.39 - 1.51 (4H, m; alifatic chain), 2 09 (1H, s(br), -OH), 2 38 (2H, q, J = 7 6 Hz, -$COCH_2CH_3$), 3 86 (1H, m, -CH(OH)-), 3 97 (1H, dd, J = 7 4 and 11 3 Hz, -CH_2O-), 4 15 (1H, dd, J = 3 0 and 11.3 Hz, -CH_2O-).

1,2-Butanediol (5)

Resolution: diol obtained by alkaline hydrolysis of the propionate, $[\alpha]^{25}_D$ +1 2° (c 1.5, ethanol), ee 9%, (*R*)-configuration; recovered diol, $[\alpha]^{25}_D$ −3 2° (c 1 4, ethanol), ee 26%, (*S*)-configuration (lit [29] for (*R*), $[\alpha]^{20}_D$ +11.92° (c 2 1, ethanol), ee 96%, lit.[30] for (*R*), $[\alpha]^{21}_D$ +12 4° (c 2 1, ethanol), ee 100%, for (*S*), $[\alpha]^{22}_D$ −12 87° (c 2 5, ethanol), ee 100%)

Monoester ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0 99 (3H, t, J = 7 5 Hz, -CH_3), 1 16 (3H, t, J = 7 6 Hz, -$COCH_2CH_3$), 1 49 - 1 55 (2H, m, -CH_2CH_3), 2 08 (1H, s(br), -OH), 2 38 (2H, q, J = 7 6 Hz, -$COCH_2CH_3$), 3 77 (1H, m, -CH(OH)-), 3 98 (1H, dd, J = 7 2 and 11 4 Hz; -CH_2O-), 4 16 (1H, dd, J = 3 1 and 11 4 Hz, -CH_2O-)

1,2-Propanediol (6)
Resolution: diol obtained by alkaline hydrolysis of the propionate, $[\alpha]^{25}_D$ −3 2° (c 0 8, chloroform), ee 10%, (*R*)-configuration, recovered diol, $[\alpha]^{25}_D$ +7 1° (c 1.0, chloroform), ee 23%, (*S*)-configuration (lit.[31] for (*R*), $[\alpha]_D$ −28 6° (chloroform), −14 9° (neat) Maximal value found[32] for (*R*), $[\alpha]^{25}_D$ +16 44° (neat) so $[\alpha]_{D,max}$ (calculated) −31.6° (chloroform)
Monoester ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1 16 (3H, t, J = 7 6 Hz; -$CH_2\underline{CH_3}$), 1 21 (3H, d, J = 6.3 Hz, -$\underline{CH_3}$), 2 26 (1H, s(br), -O$\underline{H}$), 2 39 (2H, q, J = 7 6 Hz, -$\underline{CH_2}CH_3$), 3 94 (1H, dd, J = 7 2 and 11 0 Hz, -$\underline{CH_2}$O-), 4 01 - 4 08 (1H, qdd, J = 3 1, 6 3 and 7 2 Hz, -C$\underline{H}$(OH)-), 4 11 (1H, dd, J = 3 1 and 11 0 Hz, -$\underline{CH_2}$O-).

1,3-Butanediol (7)
Resolution diol obtained by alkaline hydrolysis of the propionate, $[\alpha]^{25}_D$ −2 4° (c 1 7, ethanol), ee 8%, (*R*)-configuration, recovered diol, $[\alpha]^{25}_D$ +17 3° (c 1 1, ethanol), ee 59%, (*S*)-configuration (lit[33] for (*R*), $[\alpha]_D$ −29° (c 1, ethanol), ee 100%, for (*S*), $[\alpha]_D$ +29° (c 1, ethanol), ee 100%)
Monoester ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1 15 (3H, t, J = 7 6 Hz, -$CH_2\underline{CH_3}$), 1 23 (3H, d, J = 6 2 Hz, -$\underline{CH_3}$), 1 68 - 1 80 (2H, m, -$\underline{CH_2}$-), 2,16 (1H, s(br), -O$\underline{H}$), 2 34 (2H, q, J = 7 6 Hz, -$\underline{CH_2}CH_3$), 3 88 (1H, m, -C$\underline{H}$(OH)-), 4 13 (1H, ddd, J = 5 6, 5 7 and 11 3 Hz, -$\underline{CH_2}$O-), 4 35 (1H, ddd, J = 5 2, 8 3 and 11 3 Hz, -$\underline{CH_2}$O-)

PPL-catalyzed resolution of 1-phenyl-1,2-ethanediol (±)-1 at room temperature
PPL (5 0 g) and molecular sieves 4Å (5 0 g) were added to a solution of (±)-**1** (6 9 g, 50 0 mmol) in methyl propionate (250 ml) and the suspension was stirred for 20 h at room temperature Then the solids were filtered off and washed with ether (3x50 ml) After evaporation of the solvents, the products were separated by column chromatography (silicagel / pet ether 60 - 80°C - ethyl acetate (2 1) → (1 2)) to give 2 7 g (28%) of propionate (−)-**8** and 3 8 g (55%) of diol (+)-**1**, $[\alpha]^{25}_D$ +8 4° (c 3 0, ethanol), ee 21%, (*S*)-configuration (lit[22] for (*S*), $[\alpha]^{25}_D$ +39 3° (c 3 13, ethanol)) A small amount of the propionate was converted to the corresponding diol by alkaline hydrolysis affording pure (−)-**1**, $[\alpha]^{25}_D$ −17 5° (c 2 9, ethanol), ee 44%, (*R*)-configuration (lit[22] for (*R*), $[\alpha]^{25}_D$ −39 6° (c 2 44, ethanol))
This resolution has also been carried out under the above described conditions using (*S*)-(−)-ethyl lactate as the solvent However, after 20 h no reaction had taken place as was shown by capillary GLC and TLC

Enzymatic hydrolysis of optically enriched 2-hydroxy-2-phenyl-1-ethyl propanoate (−)-8, general procedure
A suspension of (−)-**8** (401 mg, 2 0 mmol, ee 44%) in a 0 05 M phosphate buffer (40 ml) at pH 7 0 was incubated with Mucor Esterase (100 mg) and stirred at room temperature The hydrolysis was monitored by titration with a 0 25M sodium hydroxide solution, maintaining the pH constant at 7 0 by using a pH-stat After addition of 0 5 equivalents of the sodium hydroxide solution,the reaction was stopped by extraction of the products with dichloromethane (3x30 ml) The combined extracts were dried on $MgSO_4$ and concentrated The residue gave on chromatography (silicagel / pet ether 60 - 80°C - ethyl acetate (2 1) → (1 2)) 68 mg (24%) of diol and 180 mg (45%) of remaining monopropionate, which was converted into diol by alkaline hydrolysis
This enzymatic hydrolysis has also been carried out using either PPL or PLE as the catalyst at pH 7 0 and with Mucor Esterase at pH 9 0 The results of these experiments are collected in Table 2

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