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RESOLUTION OF SECONDARY ALCOHOLS BY ENZYME-CATALYZED TRANSESTERIFICATION IN ALKYL CARBOXYLATES AS THE SOLVENT.

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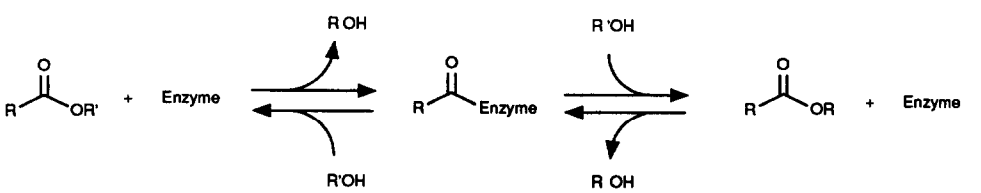
Abstract *The Porcine Pancreatic Lipase (PPL)- and Mucor Esterase-catalyzed resolution of 1-phenylethanol* **5** *in four different alkyl carboxylate solvents, viz methyl acetate, propionate and butyrate and ethyl acetate, was evaluated The beneficial influence of the addition of molecular sieves 4Å to the reaction mixture is demonstrated A Mucor Esterase-catalyzed resolution of* **5** *on a 0.5 mol scale is described The kinetic resolution of a large variety of secondary alcohols (***5** *-* **22b***) was investigated using both biocatalysts under the established optimal reaction conditions for substrate* **5**

Introduction

In the last decade the application of enzymes in organic media has been the subject of extensive investigations The state of affairs concerning this important synthetic methodology has recently been reviewed by Klibanov[1], the pioneer of biocatalysis in non-aqueous solvent systems Successful applications of various lipases (triacylglycerol hydrolases, EC 3 1 1 3), *e g* Porcine Pancreatic Lipase (PPL), Candida Cylindracea Yeast Lipase (CCL) and Pseudomonas Fluorescens (Lipase P), have been reported in carbohydrate chemistry[2-7], in peptide synthesis[8-13], and in lactonization[14-16] and macrolactonization[17-19] reactions However, the main emphasis has been on application to asymmetric esterification and transesterification reactions in order to prepare chiral alcohols[20-50] and carboxylic acids[21,22,51], or their derivatives, with high enantiomeric purity

The general sequence of transformations underlying the enzyme-catalyzed conversions is depicted in Scheme 1 The essential step is the formation of an acyl-enzyme complex Carboxylic acids (R' = H) can be used as acyl donors[24,46,50] and racemic alcohols have been resolved in this manner using lipase-catalyzed

Scheme 1



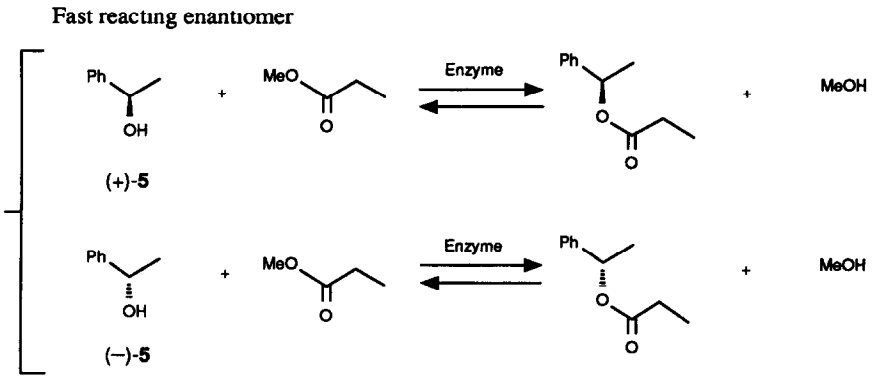
esterification reactions It seems however, that transesterification reactions using appropriate esters as acyl donor, are more versatile in terms of flexibility, reaction rates and thermodynamic limitations[28,52] For enzyme-catalyzed transesterifications Klibanov[22] recommends the use of activated esters of carboxylic acids, such as trichloroethyl and trifluoroethyl esters (R' = CCl_3CH_2 or CF_3CH_2) These esters are effective acyl donors and the released alcohol has a low nucleophilicity, which is advantageous for the position of the equilibria shown in Scheme 1 Using this methodology, a series of secondary methyl carbinols, RC(OH)Me, has successfully been resolved with PPL as the biocatalyst using ether or heptane as the main solvent[22,23,47,48] In this procedure, the products of the reaction, *viz* the remaining secondary alcohol and its ester (a butyrate when 2,2,2-trihaloethyl butyrate is used as the acyl donor), need to be separated from the excess of acyl donor and 2,2,2-trihaloethanol, which sometimes requires tedious work-up procedures In the transesterification reactions cited above, PPL is a rather sluggish biocatalyst Lipase P seems to be more effective for these transesterifications When carboxylic acid anhydrides are used as acyl donors an effective lipase-catalyzed kinetic resolution of racemic alcohols can be accomplished[28] Enol esters, such as vinyl acetate, are also interesting acyl donors[29,30,52,53], because the released vinyl alcohol tautomerizes to an aldehyde and therefore the reverse reaction is cut off However, the aldehydes may cause unwanted side reactions[28,53] It is surprising, that the use of alkyl carboxylates serving as acylating agent as well as solvent has received only scarce attention in the literature, because the position of the equilibrium of the transesterification process will be favorably influenced by the high excess of acyl donor and the experimental procedure will be attractively simple Cesti *et al*[25] described the resolution of 2,3-epoxy alcohols using PPL in ethyl acetate or methyl propionate as the reaction medium Recovered epoxy alcohol was obtained with excellent enantiomeric purity Both 1,2- and 1,3-diols are selectively esterified at the primary hydroxy group by PPL in ethyl acetate, propionate, butyrate or caprylate[54] Amino alcohols are succesfully resolved by means of PPL in methyl acetate[55,56]. It should be noted that acylation of an amino group attached to a secondary C-atom takes place at the same rate as esterification of a primary hydroxy group, whereas in the opposite situation, *i e* an amino group at a primary C-atom in the presence of a secondary hydroxy group, only the N-acylated product is found Furthermore, the excellent enantiodifferentiating ability of lipases toward meso-[52,57,58] or prochiral diols[49] in either methyl or ethyl acetate has been reported Finally, Carrea *et al*[59] described the regioselective acylation of the primary hydroxy group of chloramphenicol in methyl butyrate using Chromobacterium Viscosum as the catalyst The literature reports mentioned above, concerning the use of alkyl carboxylates as the solvent and as acylating agent at the same time, refer to lipase-catalyzed transesterifications of primary alcohol functions The reaction rate of transesterification of secondary alcohols is extremely slow under these conditions[29]

The aim of this paper is to further evaluate the use of simple alkyl carboxylates in lipase-catalyzed transesterifications of secondary alcohols where the esters serve as acylating agent as well as the solvent For this purpose, a series of chiral secondary alcohols was selected In addition to PPL, the less known enzyme Mucor Esterase[7,24,39] was used as a biocatalyst

Results and discussion

The experimental conditions were established for the commercially available substrate 1-phenylethanol (**5**) The low boiling and common solvents methyl acetate, propionate and butyrate, and ethyl acetate were considered as medium for the bioconversion reaction The processes that are involved in this kinetic resolution, are depicted in Scheme 2 (for methyl propionate as the solvent) The enantiomer that reacts fastest

Scheme 2



will be converted preferentially into the corresponding ester. If the kinetic selectivity between the enantiomers is high, the slower reacting enantiomer will remain unchanged The substrate **5** was dissolved in the ester solvent containing the enzyme (PPL) and the resulting suspension was stirred for 68 h at 40°C The products, *viz* the remaining alcohol (−)-**5** and the ester of (+)-**5**, were readily isolated as single compounds and in good yields, after filtration of the enzyme and removal of the solvent, followed by column chromatography The ester was saponified, using the procedure described by Cesti *et al* [28], to give alcohol (+)-**5** in good yields The enantiomeric purity of both alcohols (+)- and (−)-**5** was determined by comparison of their optical rotations with those reported in the literature[60] for the enantiopure compounds The PPL-catalyzed resolution of **5** was carried out in the four solvents mentioned above and under the reaction conditions given in Table 1 (entries 1, 2, 4 and 5) The results show that the enantiomeric purity of the alcohols (+)-**5** obtained after saponification of the enzymatically produced ester is high, the degree of conversion, however, is rather low Optimal results are obtained at a reaction time of 68 h at 40°C in methyl propionate (entry 2) Similarly, Mucor Esterase was evaluated as a biocatalyst Only two solvents were tested, *viz* methyl propionate and butyrate (entries 9 and 12) In comparison with PPL, Mucor exhibits a similar enantioselectivity in both solvents, but the reaction proceeds considerably faster In methyl acetate and ethyl acetate this enzyme diplays a low activity[62]

The high enantioselectivity, observed for the transesterification of alcohol **5** with both PPL and Mucor Esterase, demonstrates their resolving potential In all cases, the esters produced are isolated with high enantiomeric purity (ee ≥ 97%) These excellent results were a stimulus to optimize the reaction conditions in order to increase the conversion rate

For both enzymes the conversion could be improved only slightly by prolonging the reaction time (entries 6, 11 and 13) or increasing the reaction temperature (entries 7 and 8) This observation can be explained by assuming that the faster reacting enantiomer (see Scheme 2) reaches its state of equilibrium rather rapidly Prolonging the reaction time only brings about some further conversion of the slower reacting enantiomer and, along with this, the formation of some extra methanol which will affect the equilibrium of the faster reacting enantiomer unfavorably The ultimate consequence is that prolonged reaction times result in

Table1 Enzymatic transesterification of 1-phenylethanol (5) in alkyl carboxylates [a]

entry	solvent	temp,°C	time, h	enzyme	ester			alcohol		conv[e]
					$[\alpha]^{25}_D$[b]	ee_p[c,d]	config[d]	$[\alpha]^{25}_D$[b]	ee_s[c,d]	
1	methyl acetate	40	68	PPL	+56 1°	>98	*R*	-13.0°	23	19
2	methyl propionate	40	68	PPL	+55 9°	>98	*R*	−27 1°	48	33
3	methyl propionate (molsieves 4Å)[f]	40	68	PPL	+54 8°	97	*R*	−44 6°	79	45
4	methyl butyrate	40	68	PPL	+54 9°	97	*R*	−23 6°	42	30
5	ethyl acetate	40	68	PPL	+56 8°	>98	*R*	−15 5°	27	22
6	methyl propionate	40	164	PPL	+56 5°	>98	*R*	−36 8°	65	40
7	methyl propionate	60	68	PPL	+55.9°	>98	*R*	−31 2°	55	36
8	methyl propionate	60	164	PPL	+56 4°	>98	*R*	−39 3°	70	42
9	methyl propionate	40	68	Mucor	+56 0°	>98	*R*	−43 0°	76	44
10	methyl propionate (molsieves 4Å)[f]	40	68	Mucor[g]	+55 4°	98	*R*	−46 2°	82	45
11	methyl propionate	40	164	Mucor	+55 1°	97	*R*	−45 0°	80	45
12	methyl butyrate	40	68	Mucor	+55 6°	>98	*R*	−43 4°	77	44
13	methyl butyrate	40	164	Mucor	+54 8°	97	*R*	−42 7°	76	44

a reaction conditions 3 0 mmol of **5**, 600 mg of PPL or Mucor Esterase, 15 ml of solvent For details see experimental section.
b optical rotation (c 1, chloroform) of the alcohol obtained by hydrolysis of the ester or of the recovered alcohol
c enantiomeric excess (in %) of the alcohol obtained by hydrolysis of the ester (ee_p) or of the recovered alcohol (ee_s)
d determined by comparison of optical rotations an authentic sample of the (*S*)-isomer purchased from Aldrich with $[\alpha]^{23}_D$ −41 3° (neat) has an ee of 96% as was deduced by comparison with the rotation of enantiopure alcohol $[\alpha]^{19}_D$ +42 9° (neat), (*R*)-isomer (ref 60) This sample has $[\alpha]^{25}_D$ −54 2° (c 1, chloroform)
e conversion (in %) calculated according to the formula conv = ee_s / (ee_s + ee_p) (ref 61)
f 100 mg molecular sieves 4Å/ mmol **5**
g 50 mg Mucor Esterase / mmol **5**

less satisfactory optical yields[63] This problem can be circumvented by the addition of molecular sieves 4Å to scavenge the liberated methanol The beneficial effect of molecular sieves 4Å has also been observed by other authors[19,59] Gratifyingly, the addition of molecular sieves to the reaction mixture considerably improved the conversion after 68 h (cf entries 2 and 3, and entries 9 and 10) and consequently the enantiomeric purity of the remaining substrate alcohol (−)-**5** (82% at 45% conversion, entry 10)

These results clearly indicate that, under proper reaction conditions, both enantiomers of alcohol **5** can be obtained with a high enantiomeric excess

A procedure for a multigram scale resolution was developed for Mucor Esterase, because of its higher

activity toward **5**, compared with PPL (as judged by weights of crude enzyme per mmol of substrate, *cf* Table 1, entries 2 and 9, and entries 4 and 12) First, the amount of enzyme and solvent per unit of substrate was drastically reduced Second, the separation of the ester of (+)-**5** and remaining alcohol (−)-**5** was performed by distillation instead of chromatography For that reason methyl butyrate turned out to be the solvent of choice, because the butyrate produced and remaining alcohol (−)-**5** have the required difference in boiling point (see experimental section) It was found that at a reaction temperature of 60°C the amount of both enzyme and solvent could be reduced to 12% of their original values, still giving a conversion of 32% after 72 h It should be noted that no molecular sieves were added to the reaction mixture in order to facilitate recovery of the enzyme These conditions were found to be suitable for the resolution of 1-phenylethanol **5** on a 0 50 mol (61 1 g) scale, resulting, after work-up, in 27% of the butyrate of (+)-**5** Alkaline hydrolysis afforded (+)-1-phenylethanol in 26% overall yield and with an ee of over 98% The antipode (−)-**5** was obtained in 64% chemical yield and with an ee of 44% By repeating the enzyme treatment twice, (−)-1-phenylethanol was eventually obtained in an overall chemical yield of 36% and with an ee of 95% The procedure above is easy to perform and is therefore attractive from a practical point of view

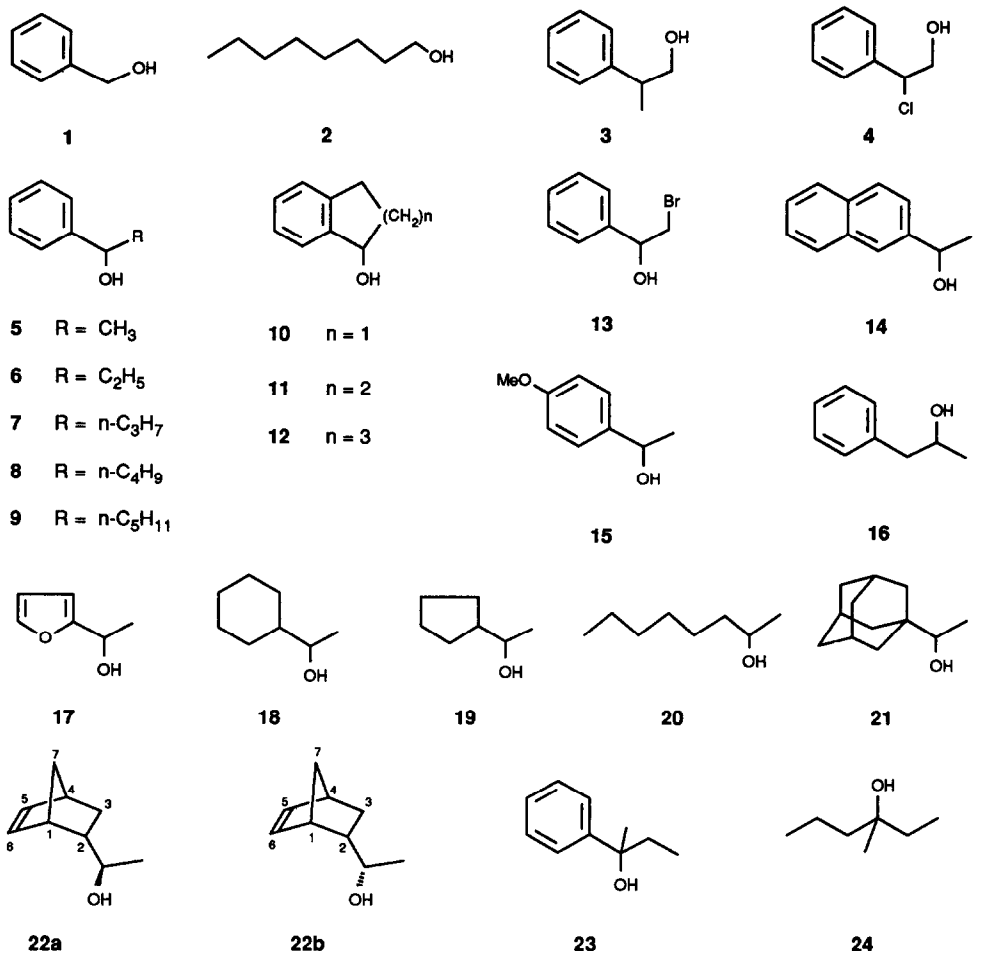
Having established the optimal reaction conditions for the resolution of **5** (methyl propionate, 68 h, 40°C, molecular sieves 4Å), the series of secondary alcohols shown in Chart 1 was subjected to the transesterification using PPL and Mucor Esterase For the sake of comparison, the primary alcohols **1** - **4** and the tertiary alcohols **23** and **24** were also investigated In all cases, the reaction mixtures were analyzed by capillary GLC before work-up When a certain conversion was considered too low, the reaction time was extended to 164 h

The substrates shown in Chart 1 were either purchased from Aldrich (**1** - **3**, **5**, **6**, **10**, **11**, **16** and **20**), or prepared by Grignard reaction[64] of appropriate alkylmagnesium halides and aldehydes or ketones (**7** - **9**, **14**, **17** - **19**, **23** and **24**), or by reduction[65] of ketones with $LiAlH_4$ (**12**, **15** and **21**) Chlorohydrin **4** was prepared by reaction of epoxy styrene with HCl in chloroform[66] and bromoalcohol **13** was readily obtained from α-bromoacetophenone by reduction[30] with $NaBH_4$ The norbornene alcohols **22a** and **22b** were prepared by Grignard reaction[64] of methylmagnesium iodide and *endo*-norborn-5-en-2-yl aldehyde, which was obtained by well established procedures[65,67-72] The results of the enzymatic resolutions are collected in Table 2

The data collected for the primary alcohols **1** - **4** reveal that, as expected, they react much faster than secondary alcohols For 2-phenyl-1-propanol **3**, the enantioselectivity of PPL is moderate (E = 10) and of Mucor Esterase rather low (E = 2) It should be noted however, that the use of PPL as catalyst affords remaining alcohol (+)-**3** nearly enantiopure Chlorohydrin **4**, which could serve as a precursor for the synthesis of optically active epoxy styrenes, is virtually not resolved by either of the enzymes

By comparing the series of secondary benzyl alcohols **5** - **9**, it is clear from the data shown, that all the esters are obtained with an excellent enantiomeric purity when PPL is employed However, the reaction rate, and accordingly the conversion, is decreasing when the carbon chain in the substrate is made longer The latter effect is even stronger when Mucor is used as the catalyst, the substrates **7** - **9** are hardly accepted by this enzyme The rigid bicyclic aromatic alcohols **10** - **12** were transesterified at a relatively high rate and with a high degree of enantioselectivity using either biocatalyst In all three cases, the propionate and the remaining alcohol were obtained with reasonable enantiomeric purity The high reaction rate exhibited by alcohols **10** - **12**, compared with substrates **5** - **9**, suggests that free rotation of the aromatic ring in the substrate has a negative influence on the reactivity Bromohydrin **13** is of interest as to provide a convenient

Chart 1



access to optically active epoxy styrenes (*cf* chlorohydrin **4**) Although the conversion is rather low employing PPL as the catalyst, the propionate of (+)-**13** was obtained with a high ee Treatment of this ester with base[28] afforded (*S*)-epoxy styrene with an ee of 95% In contrast to PPL, bromohydrin **13** is not accepted by Mucor Esterase (*cf* substrates **7** - **9**) The other secondary alcohols containing an aromatic ring, *viz* **14** - **16**, are esterified at moderate to high rates by PPL, however, in all cases the enantioselectivity is low (E = 15-30) Remarkably, compared with 1-phenylethanol **5**, PPL displays a low selectivity toward 1-(4-methoxyphenyl)-ethanol **15** (cf E = 160 for **5**, E = 30 for **15**) This difference has been observed previously for Lipase P by other authors[29], but until now an explanation has not been given Mucor shows a similar behavior toward substrates **14** and **15** 1-Phenyl-2-propanol **16**, however, is esterified at a high rate and with a high degree of enantioselectivity (E = 105) by this enzyme When the phenyl ring is replaced by the furyl ring, as in **17**, resolution leads to moderate results for both enzymes (E = 15-20) The cyclohexyl and cyclopentyl substituted

Table 2 Enzymatic resolution of primary, secondary and tertiary alcohols in methyl propionate [a]

		PPL					Mucor Esterase				
		propionate		alcohol			propionate		alcohol		
substr	time,h	ee_p[b,c]	config [d]	ee_s[b,c]	conv [e]	E[f]	ee_p[b,c]	config.[d]	ee_s[b,c]	conv [e]	E[f]
1	4	-	-	-	90[g]	-	-	-	-	97[g]	-
2	4	-	-	-	82[g]	-	-	-	-	98[g]	-
3	4	48[d]	*S*	98[d]	67	10	17[d]	*S*	35[d]	67	2
4	4	10[h]	*S*	4[h]	29	1 3	33[h]	*S*	16[h]	32	2 3
5	68	97[d]	*R*	79[d]	45	160	98[d]	*R*	82[d]	45	250
6	68	96	*R*	78	45	120	94	*R*	29	23	45
	164						94	*R*	43	31	50
7	68	93	*R*	24	20	35	-	-	-	<5[g]	-
	164	94	*R*	39	30	50					
8	68	92	*R*	14	13	25	-	-	-	<3[g]	-
	164	91	*R*	24	21	25					
9	68	93	*R*	22	18	35	-	-	-	<2[g]	-
	164	92	*R*	34	27	35					
10	68	89	*R*	89	50	50	90	*R*	90	50	60
11	68	91	*R*	89	49	65	92	*R*	83	47	65
12	68	95	*R*	48	33	65	96	*R*	53	35	85
13	68	95[h]	*S*	34[h]	27	55	-	-	-	7[j]	-
	164	95[h]	*S*	47[h]	33	60					
14	68	89[d]	*R*	52[d]	37	30	88[d]	*R*	59[d]	40	30
15	68	87[d]	*R*	72[d]	46	30	87[d]	*R*	61[d]	42	25
16	68	84	*R*	38	31	15	94	*R*	91	49	105
17	68	82[d]	*R*	63[d]	44	20	79[d]	*R*	55[d]	41	15
18	68	94	*R*	71	43	70	89	*R*	46	34	25
19	68	94	*R*[j]	54	37	50	86	*R*[j]	59	41	25
20	68	86	*R*	82	49	35	85	*R*	69	44	25
21	68	>98	*R*	18	15	>120	-	-	-	<10[g]	-

Table 2 continued.

substr.	time,h	PPL propionate ee_p[b,c]	PPL propionate config[d]	PPL alcohol ee_s[b,c]	PPL conv[e]	PPL E[f]	Mucor Esterase propionate ee_p[b,c]	Mucor Esterase propionate config[d]	Mucor Esterase alcohol ee_s[b,c]	Mucor Esterase conv[e]	Mucor Esterase E[f]
22a	68	>95	*R*[k]	~35	27	>55	>95	*R*[k]	~48	33	>60
22b	68	>95	*R*[k]	~20	17	>50	>95	*R*[k]	~29	23	>50
23	68	-	-	-	no reaction[g]	-	-	-	-	no reaction[g]	-
24	68	-	-	-	no reaction[g]	-	-	-	-	no reaction[g]	-

a. reaction conditions 3 0 mmol of substrate, 600 mg of PPL or 150 mg of Mucor Esterase, 15 ml of methyl propionate, 300 mg of molecular sieves 4Å, 40°C For details see experimental section

b enantiomeric excess (in %) of the alcohol obtained by hydrolysis of the propionate (ee_p) or of the recovered alcohol (ee_s)

c estimated by ^{19}F-NMR- or GLC-analysis of the corresponding Mosher esters, unless otherwise indicated.

d established by comparison of the optical rotation with that reported in the literature (see experimental section)

e conversion (in %) calculated according to the formula conv = ee_s / (ee_s + ee_p) (ref 61), unless indicated otherwise

f enantiomeric ratio calculated according to the formula E = ln (1 - conv (1 + ee_p)) / ln (1 - conv (1 - ee_p)) (ref 61)

g determined by capillary GLC (uncorrected)

h determined by comparison of the optical rotation of the corresponding epoxide with that reported in the literature (see experimental section)

i isolated yield

j no information known in the literature about the relation between absolute configuration and optical rotation absolute configuration based on analogy with substrates **5** - **18**, **20** and **21**

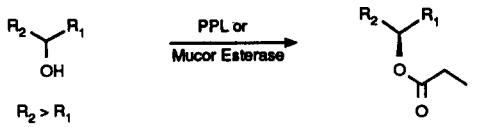
k transesterified as a mixture of both diastereomers **22a** and **22b** (62 38) no optical rotation determined, absolute configuration based on analogy with substrates **5** - **21**

carbinols **18** and **19**, respectively, as well as 2-octanol **20**, a substrate that has extensively been used in enzymatic resolutions[20,22,24,28], are readily accepted by both Mucor Esterase and PPL with moderate to good enantioselectivities (E = 35-70 for PPL, E = 25 in all three cases for Mucor) Adamantylethanol **21** apparently is too bulky to be accepted by Mucor Esterase For PPL a low conversion was observed under standard conditions, but nevertheless, the propionate of (+)-**21** was obtained with a high ee (E > 120) The norbornenyl substituted carbinols **22a** and **22b** exhibit a moderate reactivity, although these substrates are transesterified with an excellent enantioselectivity (E > 50) As shown in Table 2, tertiary alcohols do not react under the applied reaction conditions

With respect to the stereochemistry of the antipode that is preferentially esterified with these enzymes, these results show that, without exception, they all have the same basic absolute configuration, which is (*R*) for most of the alcohols Due to the presence of a bromine substituent, the propionate of bromohydrin **13** is denoted the (*S*)-configuration, but it actually has the same spatial orientation as all the other substrates

A close analysis of the results in Table 2 suggests that the high enantioselectivity observed for PPL and Mucor Esterase is caused by the difference in size of the substituents, R_1 and R_2, at the chiral center[2] (Scheme 3) An increase of the bulkiness of R_1, with R_2 is phenyl, has a negative effect on the enantioselectivity and the reactivity displayed by either catalyst (*cf* the series of substrates **5** - **9**) In the case of PPL, the efficiency of the resolution decreases enormously in the change from R_1 is ethyl (alcohol **6**) to R_1 is n-propyl (alcohol **7**), while with Mucor Esterase the efficiency already collapses by replacing the methyl substituent

Scheme 3



(alcohol **5**) by an ethyl substituent (alcohol **6**) A decrease in reactivity is also observed in the series of aromatic bycyclic substrates **10** - **12**, considering the non-aromatic ring as the R_1-substituent The mutual differences in enantioselectivity, however, are negligible The effect of R_2 on the efficiency of the enzymatic resolution of secondary alcohols is much more complicated. The relatively low enantioselectivity exhibited by the non-aromatic alcohols **18** - **20**, as compared with 1-phenylethanol **5**, demonstrates the positive impact of the phenyl group on the enantioselectivity Since the R_2-substituents in these alcohols are of comparable size, the typical electronic features of the aromatic ring may be of importance Also indicative of electronic effects is the relatively large difference in enantioselectivity observed for the 4-methoxy substituted phenylalcohol **15**, as compared with alcohol **5** Replacement of the phenyl group by the aromatic ring systems naphtyl and furyl (alcohols **14** and **17**, respectively) also leads to a decrease in E-value with both catalysts The presence of the aromatic ring adjacent to the chiral center seems to be crucial for PPL, which is not the case for Mucor Esterase (compare results for 1-phenyl-2-propanol **16** with those of 1-phenylethanol **5**) Extremely bulky R_2-substituents, such as adamantyl (alcohol **21**) or norborn-5-en-2-yl (alcohols **22a** and **22b**) strongly retard the reaction The enantioselectivity, however, is positively affected by these substituents

These extensive studies, involving the transesterification of a great variety of secondary alcohols with quite different structural features, show that both PPL and Mucor Esterase are versatile biocatalysts for this purpose Although the reaction rates in most cases are relatively low, the observed enantioselectivity is usually high enough to allow practical applications In particular, the convenience of the procedure makes resolutions with these enzymes attractive from a synthetic point of view

Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer with TMS as the internal standard ^{19}F-NMR measurements were carried out with a Bruker AM-400 spectrometer (no internal standard used) Capillary GLC analyses were performed using a HP 5790A or a HP 5890, containing a cross-linked methyl silicone column (25m) 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) was purchased from Sigma Mucor Esterase was obtained as a gift from Gist-brocades, Delft, The Netherlands Both enzymes were dried at reduced pressure (~0 02 mbar) during 4 h prior to use The solvents used for the enzymatic resolutions were stored on molecular sieves 4Å (10% w/v) All glassware was ovendried before use Substrates **1** - **3**, **5**, **6**, **10**, **11**, **16** and **20** were in stock or purchased from Aldrich

Enzymatic transesterification of 1-phenylethanol (**5**) *in methyl acetate general procedure*

Either PPL (600 mg) or Mucor Esterase (600 mg) was added to a solution of **5** (366 mg, 3.0 mmol) in methyl acetate (15 ml) The suspension was stirred magnetically for 68 h at 40°C after which the enzyme was filtered off and washed with dichloromethane (3x8 ml) After removal of the solvents 1-phenylethyl acetate and remaining alcohol were separated by column chromatography (silicagel / hexane - ethyl acetate (5 1)) The acetate was hydrolyzed to the corresponding alcohol by the procedure described by Cesti *et al* [28] as follows the acetate (164 mg, 1 0 mmol) was stirred in a 1 M solution of sodium hydroxide in ethanol (4 ml)

at room temperature during 5 h, after which the ethanol was evaporated The residue was taken up in water (5 ml) and extracted with ether (4x5 ml) The combined extracts were dried ($MgSO_4$) and concentrated Column chromatography (silicagel / hexane - ethyl acetate (5 1)) gave pure alcohol (+)-**5** in yields ranging from 85 - 90% The optical rotations ($[\alpha]^{25}_D$)of both alcohols were measured under standard conditions (c 1,chloroform)

The procedure at various temperatures and reaction times was the same as described above The results are collected in Table 1

Multigram-scale resolution of 1-phenylethanol (**5**)

Mucor Esterase (12 5 g) was added to a solution of **5** (61 1 g, 0 5 mol) in methyl butyrate (310 ml) The suspension was stirred magnetically for 76 h at 60°C, after which the enzyme was filtered off, washed with ether (3x100 ml) and stored for further use After removal of the solvents, the butyrate of (+)-**5** and remaining alcohol (–)-**5** were separated by careful distillation, furnishing 25 6 g (27%) of ester, bp 107 5 - 108°C at 6 torr (lit [73] 119 - 123°C at 14 torr), still containing 1% of alcohol (–)-**5** according to capillary GLC, and 39 0 g (64%) of alcohol, bp 83 5 - 84 5°C at 6 torr (lit [74] 98 - 99°C at 20 torr), contaminated with 1 5% of ester A sample of alcohol (–)-**5** was purified by column chromatography (silicagel / hexane - ethyl acetate (5 1)) affording pure (–)-**5**, $[\alpha]^{25}_D$ –19 1° (neat) (lit [60] $[\alpha]^{19}_D$ +42 9° (neat)), ee 44%

Alcohol (+)-**5** was obtained as follows the butyrate of (+)-**5** (25 g, 0 13 mol) was stirred for 6 h at room temperature in a 1 M solution of sodium hydroxide in ethanol (425 ml) Ethanol was evaporated, the residue was taken up in water (200 ml) and extracted with ether (4x125 ml) The combined extracts were dried ($MgSO_4$) and concentrated Distillation of the remaining liquid furnished 15 4 g (97%) of pure alcohol (+)-**5**, bp 66 5 - 67°C at 2 torr, $[\alpha]^{25}_D$ +42 5° (neat), ee >98%

A higher ee of alcohol (–)-**5** was obtained by subjecting it to a second [on 30 5 g (0 25 mol) scale] and a third [on 12 5 g (0 1 mol) scale] resolution following the same procedure as for racemic **5** and using recovered enzyme from the first and second resolution, respectively In this manner, (–)-**5** (10 5 g) with an ee of 95% was obtained, $[\alpha]^{25}_D$ –40 7° (neat)

Substrates **7** - **9**, **14**, **17** - **19**, **23** *and* **24** *were prepared by Grignard reaction*[64]

1-Phenyl-1-butanol (**7**) *general procedure*

A solution of benzaldehyde (10.6 g, 0 10 mol) in ether (50 ml) was slowly added at room temperature to a Grignard reagent (prepared from magnesium (3.0 g, 0 125 mol) and n-propyl bromide (15 4 g, 0 125 mol) in ether (50 ml)) in such a manner that a gentle reflux was maintained The reaction mixture was stirred over night at room temperature, then saturated NH_4Cl (125 ml) was slowly added at 0°C Stirring was continued for another 10 min at room temperature, then the aqueous layer was extracted with ether (2x50 ml) The combined extracts were successively washed with saturated $Na_2S_2O_5$ (15 ml), saturated $NaHCO_3$ (15 ml) and water (2x25 ml), dried on $MgSO_4$ and concentrated The residual oil was distilled to furnish 12 0 g (80%) of **7**, bp 72 - 74°C at 3 5 torr (lit [75] 113 - 115°C at 17 torr) A sample was also purified by column chromatography (silicagel / hexane - ethyl acetate (12 1)) IR(CCl_4) ν 3610(s), 3600-3200 (s,br), 3080 / 3060 / 3030 (m), 2960 / 2930 / 2870 (s), 1950 / 1880 / 1805 (w), 1455 (s), 700 (s) cm^{-1} ^{1}H-NMR($CDCl_3$) δ 0 91 (3H, t, J=7 0Hz, $CH_2\underline{CH_3}$), 1 15 - 1 54 (2H, m, $\underline{CH_2}CH_3$), 1 55 - 1 89 (2H, m, $CH(OH)\underline{CH_2}$), 2 00 (1H, s, O<u>H</u>), 4 67 (1H, t, J=6 5Hz, C<u>H</u>(OH)), 7 30 (m, 5ArH)

1-Phenyl-1-pentanol (**8**)

Prepared from n-butyl bromide (17 1 g, 0 125 mol) and benzaldehyde (10 6 g, 0 10 mol) furnishing 13 6 g (83%) of **8** (oil), bp 69 - 71°C at 1 torr (lit [76] 124 - 126°C at 10 torr) A sample was also purified by column chromatography (silicagel / hexane - ethyl acetate (12 1)) IR(CCl_4) ν 3610 (s), 3600-3200 (s,br), 3080 / 3060 / 3030 (m), 2960 - 2920 / 2870 (s), 1950 / 1880 / 1810 (w), 1455 (s), 700 (s) cm^{-1} ^{1}H-NMR($CDCl_3$)[76] δ 0 90 (3H, t, J=6 0Hz, $CH_2\underline{CH_3}$), 1 15 - 1 52(4H, m, $\underline{CH_2}CH_2CH_3$), 1 62 - 1 87 (2H, m, $CH(OH)\underline{CH_2}$), 1 94 (1H, s, O<u>H</u>), 4 64 (1H, t, J=6 5Hz, C<u>H</u>(OH)), 7 32 (m, 5ArH)

1-Phenyl-1-hexanol (**9**)

Prepared from n-pentyl bromide (18 9 g, 0 125 mol) and benzaldehyde (10 6 g, 0 10 mol) affording 13 6 g (76%) of pure **9** (oil), bp 102 - 104°C at 2 torr (lit [77] 170°C at 50 torr) IR(CCl_4) ν 3610 (s), 3550-3250 (m,br), 3080 / 3060 / 3030 (m), 2960 / 2920 / 2860 (s), 1950 / 1880 / 1810 (w), 1450 (m), 700 (s) cm^{-1} ^{1}H-NMR($CDCl_3$) δ 0 87 (3H, t, J=6 0Hz, $CH_2\underline{CH_3}$), 1 18 - 1 47 (6H, m, $(\underline{CH_2})_3CH_3$), 1 62 - 1 82 (2H, m, $CH(OH)\underline{CH_2}$), 2 02 (1H, s, O<u>H</u>), 4 63 (1H, t, J=6 0Hz, C<u>H</u>(OH)), 7 29 (m, 5ArH)

1-(2-Naphtyl)ethanol (**14**)

Prepared from methyl iodide (5 7 g, 40 mmol) and 2-naphtaldehyde (5 0 g, 32 mmol) giving, after column chromatography (silicagel / hexane - ethyl acetate (9 1)), 5 0 g (90%) of a white solid, mp 67 - 70°C

(lit [78] 71 - 72°C) IR(CCl_4) ν 3610 (s), 3550 - 3250 (m,br), 3060 (s), 3020 (w), 2980 (s), 2930 / 2880 (w), 1450 (w), 860 (s) cm^{-1} ^{1}H-NMR($CDCl_3$) δ 1 56 (3H, d, J=6.5Hz, CH_3), 2 09 (1H, s, OH), 5 04 (1H, q, J=6 5Hz, CH(OH)), 7.40 - 7 53 (m, 3ArH), 7 73 - 7 86 (m,4ArH)

1-(2-Furfuryl)ethanol (**17**)

Prepared from methyl iodide (9 2 g, 65 mmol) and 2-furfuraldehyde (5 0 g, 52 mmol) furnishing, after column chromatography (silicagel / hexane - ethyl acetate (7 1)), 4 3 g (74%) of **17** (oil) IR(CCl_4) ν 3610 (s), 3600 - 3100 (s,br), 2990 (s), 2930 / 2880 (m), 1740 (m) cm^{-1} ^{1}H-NMR($CDCl_3$)[79] δ 1 52 (3H, d, J=6 5Hz, CH_3), 2 50 (1H, s, OH), 4 87 (1H, q, J=6 5Hz, CH(OH)), 6 21 (1H, d, J=3 5Hz, furan-H_3), 6 31 (1H, dd, J=3 5 and 1 0Hz, furan-H_4), 7 37 (1H, d, J=1 0Hz, furan-H_5)

1-(Cyclohexyl)ethanol (**18**)

Prepared from cyclohexyl chloride (14 8 g, 0 125 mol) and acetaldehyde (4 4 g, 0 10 mol) affording 12 1 g (95%) of crude **18** (oil), bp 82 - 91°C at 25 torr (lit [80] 81 - 82°C at 15 torr) Subsequent column chromatography (silicagel / hexane - ethyl acetate (5 1)) gave 9 6 g (75%) of pure **18** (oil) IR(CCl_4) ν 3610 (s), 3550 - 3250 (s,br), 2960 - 2900 / 2850 (s), 1450 (s) cm^{-1} ^{1}H-NMR($CDCl_3$)[81] δ 0 73 - 1 88 (12H, m, c-C_6H_{11} and OH), 1 16 (3H, d, J=6 0Hz, CH_3), 3 54 (1H, dq, J=6 0 and 6 0Hz, CH(OH))

1-(Cyclopentyl)ethanol (**19**)

Prepared from cyclopentyl bromide (9 3 g, 62 5 mmol) and acetaldehyde (2 8 g, 62 5 mmol) resulting, after column chromatography (silicagel / hexane - ethyl acetate (5 1)), in 2 8 g (41%) of pure **19** (oil) IR(CCl_4) ν 3620 (s), 3550 - 3200 (s,br), 2980 - 2920 / 2860 (s), 1450 (s) cm^{-1} ^{1}H-NMR($CDCl_3$)[82] δ 1 20 (3H, d, J=6 0Hz, CH_3),1 30 - 1 84 (10H, m, c-C_5H_9 and OH), 3 57 (1H, dq, J=6 0 and 6 0Hz, CH(OH))

2-Phenyl-2-butanol (**23**)

Prepared from bromobenzene (19 6 g, 0 125 mol) and 2-butanone (7 2 g, 0 10 mol) furnishing 11 2 g (75%) of **23** (oil), bp 86 - 88°C at 10 torr (lit [83] 97°C at 15 torr) A sample was purified by column chromatography (silicagel / hexane - ethyl acetate (9 1)) IR(CCl_4) ν 3600 (s), 3600 - 3200 (m,br), 3080 / 3060 / 3030 (m), 2970 / 2930 / 2880 (s), 1900 / 1880 / 1800 (w), 1445 (s), 700 (s) cm^{-1} ^{1}H-NMR($CDCl_3$) δ 0 79 (3H, t, J=7 5Hz, CH_2CH_3), 1 54 (3H, s, C(CH_3)(OH)), 1 80 (1H, s(br), OH), 1.83 (2H, q, J=7 5Hz, CH_2CH_3), 7 15 - 7 51 (m, 5ArH)

3-Methyl-3-hexanol (**24**)

Prepared from 2-pentanone (4 1 g, 48 mmol) and ethyl bromide (6 5 g, 60 mmol) furnishing, after column chromatography (silicagel / hexane - ethyl acetate (7 1)), 4 5 g (81%) of **24** (oil) IR(CCl_4) ν 3610 (s), 3600 - 3200 (s,br), 2980 - 2870 (s,br), 1460 (s) cm^{-1} ^{1}H-NMR($CDCl_3$) δ 0 82 - 1 01 (6H, m, 2xCH_2CH_3), 1 16 (3H, s, CH(OH)CH_3), 1 27 (1H, s, OH), 1 31 - 1 62 (6H, m, all CH_2)

Alcohols **12**, **15** *and* **21** *were prepared by* $LiAlH_4$ *reduction*[65] *of the corresponding ketones*

6,7,8,9-Tetrahydro-5-H-benzocyclohepten-5-ol (**12**) *general procedure*

To a suspension of $LiAlH_4$ (1 5 g, 39 mmol) in ether (50 ml) a solution of benzosuberon (5 3 g, 33 mmol, obtained from Aldrich) in ether (50 ml) was slowly added in such a manner that a gentle reflux was maintained The reaction mixture was stirred at room temperature for 2 h after which at 0°C water (3 ml), a 15% solution of potassium hydroxide (3 ml) and water (3 ml) were carefully added followed by $MgSO_4$ After stirring for 1 5 h at room temperature, the solids were filtered off and washed with ether (3x50 ml) The organic solution was dried on $MgSO_4$ and concentrated to give 5 2 g (98%) of **12**, mp 99 - 100°C (lit [84] 100 - 101°C) IR(CCl_4) ν 3590 (s), 3650 - 3200 (s,br), 3080 - 3000 (w), 2910 / 2850 (s), 1440 (m) cm^{-1} ^{1}H-NMR($CDCl_3$) δ 1 37 - 2 07 (7H, m, CH(OH)$CH_2(CH_2)_3$), 2 54 - 3 07 (2H, m, CH(OH)CH_2), 4 90 (1H, dd, J=2 5 and 5 0Hz, CH(OH)), 7 00 - 7 50 (m, 4ArH)

1-(4-Methoxy-phenyl)ethanol (**15**)

Prepared from 4-methoxy acetophenone (15 0 g, 0 10 mol) furnishing 15 2 g (100%) of pure **15** IR(CCl_4) ν 3610 (s), 3650 - 3150 (s,br), 3100 / 3070 / 3030 (w), 3000 - 2870 (s,br), 2835 (s), 1610 (s), 1460 (s) cm^{-1} ^{1}H-NMR($CDCl_3$)[85] δ 1 44 (3H, d, J=6 5Hz, CH(OH)CH_3), 2 43 (1H, s, OH), 3 77 (3H, s, OCH_3), 4 80 (1H, q, J=6 5Hz, CH(OH)), 6 84 (dt, J=8 5 and 2 5Hz, 2ArH), 7 27 (dt, J=8 5 and 2 5Hz, 2ArH)

1-(1-Adamantyl)ethanol (**21**)

Prepared from 1-adamantyl methyl ketone (2 3 g, 13 mmol) furnishing after column chromatography (silicagel / hexane - ethyl acetate (7 1)) 1 5 g (98%) of **21**, mp 76 - 77°C (lit [86] 75 - 76°C) IR(CCl_4) ν 3630 (m), 3600 - 3300 (w,br), 2980 - 2840 (s,br), 1450 (m) cm^{-1} ^{1}H-NMR($CDCl_3$) δ 1 10 (3H, d, J=6 5Hz,

$CH(OH)C\underline{H}_3$), 1 39 (1H, s(br); O$\underline{H}$), 1,51 (6H, s(br), $C\underline{H}_2$), 1,67 (6H, s(br), $C\underline{H}_2$), 2.00 (3H, s(br), 3°C$\underline{H}$), 3 30 (1H, q, J=6,5Hz, C$\underline{H}$(OH))

2-Chloro-2-phenylethanol (**4**)

This alcohol was prepared in a yield of 49% by reaction of HCl with epoxy styrene[66], bp 72 - 73°C at 0.15 torr (lit.[66] 86°C at 1 torr) IR (CCl_4) ν: 3600 (s), 3650 - 3200 (s,br), 3090 / 3060 / 3040 (s), 2960 / 2920 / 2870 (s), 1950 / 1870 / 1800 (w), 1450 (s), 1380 (s), 1250 (s), 1080 - 1020 (s,br), 700 (s) cm^{-1} ^{1}H-NMR ($CDCl_3$) δ. 2,45 (1H, s, O$\underline{H}$), 3.87 (2H, d, J=7 0 Hz; $C\underline{H}_2$OH), 4.90 (1H, t, J=7 0 Hz, C$\underline{H}$Cl), 7.33 (m, 5 ArH).

2-Bromo-1-phenylethanol (**13**)

This compound was prepared in a yield of 97% by $NaBH_4$ reduction of α-bromo-acetophenone according to the procedure described by Hiratake *et al.*[30] Column chromatography (silicagel / hexane - ethyl acetate (9.1)) furnished **13** as a colourless oil which solidified upon standing at -10°C IR(CCl_4) ν: 3560 (s), 3600 - 3300 (m,br), 3080 / 3060 / 3020 (m), 2960 / 2880 (m), 1950 / 1880 / 1800 (w), 1450 (m), 700 (s) cm^{-1} ^{1}H-NMR($CDCl_3$)[87,88] δ: 2.87 (1H, s(br); O$\underline{H}$), 3.49 (1H, dd, J=8.0 and 10Hz, $C\underline{H}_2$Br), 3 63 (1H, dd, J=5.0 and 10Hz, $C\underline{H}_2$Br), 4 89 (1H, dd, J=5 0 and 8 0Hz; C$\underline{H}$(OH)), 7 31 (m, 5ArH)

2-endo-*(1-hydroxyethyl)-bicyclo[2 2 1]hept-5-ene* (**22a** *and* **22b**)

This alcohol was prepared according to literature procedures· Diels-Alder addition of acrylic acid and cyclopentadiene[67,68], *endo/exo* separation by iodolactonization[69,70] followed by zinc - acetic acid reduction[71] of the iodolactone gave pure *endo*-bicyclo[2.2.1]hept-5-ene 2-carboxylic acid. $LiAlH_4$ reduction[65] of this acid, subsequent Swern oxidation[72] and finally Grignard addition[64] of methylmagnesium iodide and the aldehyde obtained, furnished a pure colorless oil which, according to capillary GLC, consisted of diastereomers **22a** and **22b** (62.38). By comparison of the 90 MHz NMR spectrum with literature data[89] structure **22a** was assigned to the major diastereomer and structure **22b** to the minor one IR(CCl_4) ν· 3620 (m), 3600 - 3100 (s,br), 3060 (m), 2980 - 2920 (s), 2870 (s), 1450 (m) cm^{-1} ^{1}H-NMR($CDCl_3$) δ. (mixture of **22a** and **22b**) 0 50 and 0.93 (1H ,m, H_3(*endo*)), 1.13 and 1.23 (3H, d ,J=6 0Hz; $C\underline{H}_3$), 1 28 - 1 53 (2H, m, 2xH_7), 1,63 - 2 13 (2H, m, H_2(*exo*) and H_3(*exo*)), 2 77 - 3 17 (3H, m; H_1, H_4 and C$\underline{H}$(OH)), 5 88 and 6.00 (1H, dd, J=3 0 and 5 5Hz, H_6), 6 15 (1H, dd, J=3 0 and 5 5Hz, H_5)

Enzymatic transesterification of substrates **1** - **24**

Substrates **1** - **24** were transesterified either by PPL or Mucor Esterase in methyl propionate as the solvent by the procedure described below. The alkaline hydrolyses of the propionates of alcohols **3** - **22b** were carried out following the general procedure described below for **5**. The essential data, such as reaction time, conversion, ee's, absolute configuration and enantiomeric ratio, are collected in Table 2 Optical rotations ($[\alpha]^{25}_D$) are given below

Enzymatic transesterification of 1-phenyl-ethanol (**5**) *and alkaline hydrolysis general procedure*

Molecular sieves 4Å (300 mg) and either PPL (600 mg) or Mucor Esterase (150 mg) were added to a solution of **5** (366 mg, 3 0 mmol) in methyl propionate (15 ml) The suspension was stirred magnetically for 68 h at 40°C after which enzyme and molecular sieves were filtered off and washed with dichloromethane (3x8 ml) After evaporation of the solvents, the propionate of (+)-**5** and remaining alcohol (−)-**5** were separated by column chromatography (silicagel / hexane - ethyl acetate (5 1)) The propionate (178 mg, 1 mmol) was saponified at room temperature with a 1 M solution of sodium hydroxide in ethanol (4 ml) during 5 h, after which the ethanol was evaporated The residue was taken up in water (5 ml) and extracted with ether (4x5 ml) The extracts were dried ($MgSO_4$) and concentrated Column chromatography (silicagel / hexane - ethyl acetate (5 1)) gave alcohol (+)-**5**

Synthesis of the α-methoxy-α-trifluoromethyl-α-phenyl acetates general procedure [28,90]

(+)-α-Methoxy-α-trifluoromethyl-α-phenylacetyl chloride (32 mg, 0 125 mmol) was added to a solution of **5** (12 2 mg, 0 10 mmol) and dry pyridine (10 drops) in carbon tetrachloride (10 drops). The reaction mixture was stirred over night at room temperature, then diluted with ether (5 ml) and washed successively with 2 M HCl (3 ml), brine (3 ml), saturated $NaHCO_3$ (3 ml) and brine (3 ml) and finally dried on $MgSO_4$ GLC showed that no starting material was present anymore

For compounds **10** to **12** and **21** to **22b** the diastereomeric MTPA-esters were analyzed by capillary GLC, the ee was determined by integration of the respective signals For all other compounds the MTPA-esters were dissolved in $CDCl_3$ for ^{19}F-NMR analysis Ee's were determined by integration of the CF_3 signals When integration was not possible (either due to small impurities which interfered with the CF_3 signals or incomplete separation of the signals), ee's were determined by comparison of optical rotations with literature data (**3**, **5**, **14**, **15** and **17**).

For compounds **4** and **13** the ee's were determined after conversion of the remaining alcohol and the propionate into the corresponding epoxides, as described by Itsuno et al.[91]. (*R*)-2-bromo-1-phenylethanol (2 0 g, 10 mmol) in ether (10 ml) was stirred for 3 h with a 2 M solution of sodium hydroxide (10 ml) at 0°C The aqueous layer was extracted with ether (3x10 ml). The extracts were dried on $MgSO_4$ and concentrated Column chromatography (silicagel / hexane - ethyl acetate(9:1)) gave 1.1 g (92%) of a colourless oil IR(CCl_4) ν 3090 / 3060 / 3040 (s), 2990 (s), 2910 (w), 1900 / 1880 / 1810 (w), 1450 (m), 880 (s), 700 (s) cm^{-1} ^{1}H-NMR($CDCl_3$)[92] δ 2 80 (1H, dd, J=2 5 and 5 5Hz; CH_2O), 3 14 (1H, dd, J=4 0 and 5.5Hz, CH_2O), 3.84 (1H, dd, J=4 0 and 2 5Hz; CHO), 7 31 (m, 5ArH). The propionate (1.3 g, 5 mmol) was stirred for 3 h at room temperature in a 1 M solution of sodium hydroxide in ethanol (15 ml). After 5 h the ethanol was evaporated, the residue was taken up in water (10 ml) and extracted with ether (4x10 ml). The extracts were dried on $MgSO_4$ and concentrated Column chromatography (silicagel / hexane - ethyl acetate (9:1)) furnished 0 42 g (71%, not optimized) of pure (*S*)-epoxy styrene (oil). Spectral data were identical with those of (*R*)-epoxy styrene Optical rotations of (*R*)- and (*S*)-epoxy styrene are given below

2-Phenyl-1-propanol (**3**)
PPL(4h)· alcohol obtained from the propionate, $[\alpha]^{25}_D$ −6.4° (c 1, $CHCl_3$), −7 6° (neat), ee 48%, (*S*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +13 6° (c 1, $CHCl_3$), +15 5° (neat), ee 98%, (*R*)-configuration
Mucor(4h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −2 4° (c 1.1, $CHCl_3$), −2.7° (neat), ee 17%, (*S*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ +3 3° (c 1, $CHCl_3$), +5 6° (neat), ee 35%, (*R*)-configuration
Literature.[93] for (*R*), $[\alpha]^{20}_D$ +15 75° (neat), for (*S*), $[\alpha]^{19}_D$ −15 67° (neat).

2-Chloro-2-phenylethanol (**4**)
PPL (4h) epoxide obtained from the propionate, $[\alpha]^{25}_D$ −4 1° (c 1 1, benzene), ee 10%, (*S*)-configuration, epoxide obtained from the recovered alcohol, $[\alpha]^{25}_D$ +1 7° (c 1 2, benzene), ee 4%, (*R*)-configuration
Mucor (4h)· epoxide obtained from the propionate, $[\alpha]^{25}_D$ −14 1° (c 1.0, benzene), ee 33%, (*S*)-configuration, epoxide obtained from the recovered alcohol, $[\alpha]^{25}_D$ +6.8° (c 0 9, benzene), ee 16%, (*R*)-configuration.
Literature·[87] for (*R*)-epoxy styrene, $[\alpha]^{25}_D$ +42 2° (c 3 1, benzene), ee 95%

1-Phenylethanol (**5**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +54 8° (c 0 9, $CHCl_3$), ee 97%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −44 6° (c 1, $CHCl_3$), ee 79%, (*S*)-configuration
Mucor(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +55 4° (c 1 1, $CHCl_3$), ee 98%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −46 2° (c 1, $CHCl_3$), ee 82%, (*S*)-configuration
Literature An authentic sample purchased from Aldrich, $[\alpha]^{23}_D$ −41 3° (neat), ee 96% (cf literature[60], $[\alpha]^{19}_D$ +42 9° (neat)), had an $[\alpha]^{25}_D$ +54 2° (c 1, $CHCl_3$)

1-Phenyl-1-propanol (**6**)
PPL(68h). alcohol obtained from the propionate, $[\alpha]^{25}_D$ +49 0° (c 1, $CHCl_3$), +46 9° (c 1, acetone), ee 96%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −37 0° (c 1, $CHCl_3$), −35 9° (c 1 1, acetone), ee 78%, (*S*)-configuration
Mucor(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +46 7° (c 0 8, $CHCl_3$), +44 9° (c 0 7, acetone), ee 94%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −14 3° (c 1 1, $CHCl_3$), −13 7° (c 1, acetone), ee 29%, (*S*)-configuration
Mucor(164h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +47 4° (c 1 1, $CHCl_3$), ee 94%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −21 0° (c 1 1, $CHCl_3$), ee 43%, (*S*)-configuration
Literature [91] for (*R*), $[\alpha]_D$ +44 2° (acetone), ee 94%

1-Phenyl-1-butanol (**7**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +49 8° (c 1, $CHCl_3$), ee 93%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −11 6° (c 1, $CHCl_3$), −10 5° (c 5, benzene), ee 24%, (*S*)-configuration
PPL(164h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +50 6° (c 1, $CHCl_3$), ee 94%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −18 4° (c 1, $CHCl_3$), −16 6° (c 4 9, benzene), ee 39%, (*S*)-configuration
Literature [91,94] (a) for (*R*), $[\alpha]_D$ +43 4° (benzene), ee 96%, for (*S*), $[\alpha]_D$ −41 3° (benzene), ee 91%, (b) for (*S*), $[\alpha]_D$ −45 2° (c 4 8, benzene), ee 100%

1-Phenyl-1-pentanol (**8**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +40.3° (c 0 8, $CHCl_3$), ee 92%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −5 3° (c 1 1, $CHCl_3$), ee 14%, (*S*)-configuration
PPL(164h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +40 5° (c 1, $CHCl_3$), ee 91%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −9 0° (c 1 1, $CHCl_3$), −4 2° (neat), ee 24%, (*S*)-configuration
Literature [91] for (*R*), $[\alpha]_D$ +20 0° (neat), ee 100%

1-Phenyl-1-hexanol (9)
PPL(68h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +34.6° (c 0 9, $CHCl_3$), ee 93%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −7.1° (c 1, $CHCl_3$), −5.8° (c 5.8, cyclopentane), ee 22%, (*S*)-configuration.
PPL(164h). alcohol obtained from the propionate, $[\alpha]^{25}_D$ +35 6° (c 1, $CHCl_3$), ee 92%, (*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ −12.0° (c 1, $CHCl_3$), −10.2° (c 5.3, cyclopentane), ee 34%, (*S*)-configuration
Literature.[95] for (*R*), $[\alpha]_D$ +2 86° (c 5 71, cyclopentane), ee 13%

1-Indanol (10)
PPL(68h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ −29 8° (c 1 1, $CHCl_3$), ee 89%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +28.8° (c 1 1, $CHCl_3$), ee 89%, (*S*)-configuration.
Mucor(68h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ −29.0° (c 1, $CHCl_3$), ee 90%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +27.2° (c 1, $CHCl_3$), ee 90%, (*S*)-configuration
Literature[96] for (*R*), $[\alpha]^{30}_D$ −29° (c 2, $CHCl_3$), ee not specified, for (*S*), $[\alpha]^{20}_D$ +30° (c 2, $CDCl_3$), ee not specified

1-Tetralol (11)
PPL(68h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ −31 3° (c 1 1, $CHCl_3$), ee 91%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +30.4° (c 1, $CHCl_3$), ee 89%, (*S*)-configuration
Mucor(68h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ −30.8° (c 1 1, $CHCl_3$), ee 92%, (*R*)-configuration; recovered alcohol, $[\alpha]^{25}_D$ +27 2° (c 1.1, $CHCl_3$), ee 83%, (*S*)-configuration
Literature [97] for (*R*), $[\alpha]^{17}_D$ −32° (c 2 5, $CHCl_3$), ee not specified, for (*S*), $[\alpha]^{17}_D$ +32° (c 2 5, $CHCl_3$), ee not specified

6,7,8,9-Tetrahydro-5-H-benzocyclohepten-5-ol (12)
PPL(68h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +33 4° (c 1, $CHCl_3$), ee 95%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −13 8° (c 1, $CHCl_3$), 48% ee, (*S*)-configuration
Mucor(68h). alcohol obtained from the propionate, $[\alpha]^{25}_D$ +34 1° (c 1, $CHCl_3$), ee 96%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −18 8° (c 1, $CHCl_3$), ee 53%, (*S*)-configuration
Literature [98] for (*S*), $[\alpha]_D$ −26 6° (c 4, $CHCl_3$), ee not specified

2-Bromo-1-phenylethanol (13)
PPL(68h). epoxide obtained from the propionate, $[\alpha]^{25}_D$ −43 5° (c 0 8, benzene), ee 95%, (*S*)-configuration, epoxide obtained from the recovered alcohol, $[\alpha]^{25}_D$ +15 1° (c 3 5, benzene), +15 7° (c 0 7, benzene), ee 34%, (*R*)-configuration
PPL(164h) epoxide obtained from the propionate, $[\alpha]^{25}_D$ −42 4° (c 3 8,benzene), ee 95%, (*S*)-configuration, epoxide obtained from the recovered alcohol, $[\alpha]^{25}_D$ +21 0° (c 3 7, benzene), ee 47%, (*R*)-configuration
Literature [87] for (*R*)-epoxy styrene, $[\alpha]^{25}_D$ +42 2° (c 3 1, benzene), ee 95%

1-(2-Naphtyl)ethanol (14)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +49 6° (c 1 1, $CHCl_3$), ee 89%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −29 2° (c 1, $CHCl_3$), ee 52%, (*S*)-configuration
Mucor(68h): alcohol obtained from the propionate, $[\alpha]^{25}_D$ +49 1° (c 1 1, $CHCl_3$), ee 88%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −33 0° (c 1 1, $CHCl_3$), ee 59%, (*S*)-configuration
Literature [78] for (*R*), $[\alpha]_D$ +55 8° ($CHCl_3$), ee not specified

1-(4-Methoxy-phenyl)-ethanol (15)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +52 1° (c 1, $CHCl_3$), +43 6° (c 1 1, benzene), ee 87%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −41 9° (c 1 1, $CHCl_3$), −36 0° (c 1 1, benzene), ee 72%, (*S*)-configuration
Mucor(68h). alcohol obtained from the propionate, $[\alpha]^{25}_D$ +51 8° (c 1, $CHCl_3$), +43 6° (c 1 1, benzene), ee 87%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −37 2° (c 1 2, $CHCl_3$), −30 4° (c 1, benzene), ee 61%, (*S*)-configuration
Literature [99] for (*R*), $[\alpha]_D$ +50 3° (benzene), ee 100%

1-Phenyl-2-propanol (16)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −35 1° (c 1, $CHCl_3$), ee 84%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +15 6° (c 1, $CHCl_3$), +15 8° (c 4 7, benzene), ee 38%, (*S*)-configuration
Mucor(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −39 3° (c 1 1, $CHCl_3$), ee 94%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +35 8° (c 1 1, $CHCl_3$), ee 91%, (*S*)-configuration
Literature [100] for (*S*), $[\alpha]^{20}_D$ +17 0° (c 5 8, benzene), ee 41%

1-(2-Furfuryl)ethanol (**17**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +18 6° (c 1 1, $CHCl_3$), ee 82%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −14.4° (c 1 1, $CHCl_3$), ee 63%, (*S*)-configuration
Mucor(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +18 0° (c 1, $CHCl_3$), ee 79%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −12 5° (c 1.1, $CHCl_3$), ee 55%, (*S*)-configuration
Literature [101] for (*R*), $[\alpha]_D$ +5 0° (c 3 1, $CHCl_3$), ee 22%

1-(Cyclohexyl)ethanol (**18**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −3.4° (c 1.1, $CHCl_3$), ee 94%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +2 8° (c 1 1, $CHCl_3$), ee 71%, (*S*)-configuration
Mucor(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −3 0° (c 1, $CHCl_3$), ee 89%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +1 4° (c 1 1, $CHCl_3$), +2 3° (neat), ee 46%, (*S*)-configuration
Literature [100] for (*S*), $[\alpha]^{20}_D$ +0 182 (l=0 1, neat), ee 35%

1-(Cyclopentyl)ethanol (**19**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −20 2° (c 0 9, $CHCl_3$), ee 94%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +12 2° (c 1, $CHCl_3$), ee 54%, (*S*)-configuration
Mucor(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −18 2° (c 1, $CHCl_3$), ee 86%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +10 9° (c 1, $CHCl_3$), ee 59%, (*S*)-configuration
Literature for this compound no optical rotations are known in the literature absolute configuration based on comparison with compounds **5** to **18** and **20**, **21**

2-Octanol (**20**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −8 1° (c 1, $CHCl_3$), ee 86%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +7 9° (c 1.1, $CHCl_3$), +8 9° (c 3 2, ethanol), ee 82%, (*S*)-configuration
Mucor(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ −7 9° (c 1 1, $CHCl_3$), ee 85%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ +6 2° (c 1, $CHCl_3$), ee 69%, (*S*)-configuration
Literature [91] for (*R*), $[\alpha]_D$ −5 86° (ethanol), ee 58%

1-(1-adamantyl)ethanol (**21**)
PPL(68h) alcohol obtained from the propionate, $[\alpha]^{25}_D$ +1 6° (c 0 4, $CHCl_3$), ee >98%, (*R*)-configuration, recovered alcohol, $[\alpha]^{25}_D$ −0 4° (c 1, $CHCl_3$), ee 18%, (*S*)-configuration, acetate of recovered alcohol, $[\alpha]^{25}_D$ −3 3° (c 2 6, CCl_4)
Literature [102] for the alcohol no optical rotations are available in the literature, acetate, for (*R*), $[\alpha]_D$ +18 1° (c 3 8, CCl_4), ee 97 7%

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