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ENZYMATIC RESOLUTION OF BUTANOIC ESTERS OF 1-PHENYL, 1-PHENYLMETHYL, 1-[2-PHENYLETHYL] AND 1-[2-PHENOXYETHYL] ETHERS OF 3-METHOXY-1,2-PROPANEDIOL

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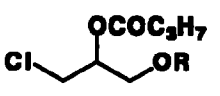
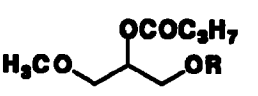
Abstract: The enzymatic hydrolysis of butanoic esters of 1-phenyl-, 1-phenylmethyl-, 1-[2-phenylethyl] and 1-[2-phenoxyethyl] ethers of 3-methoxy-1,2-propanediol has been studied by using lipases. Highest enantioselectivity *E* was obtained with Amano PS lipase for the phenyl ether $E \approx 55$, and with lipase B from *Candida antarctica* for the other derivatives, $E \approx 20$, >100 and >55 respectively. The absolute configurations of the products were verified from comparison with reference compounds synthesised from *(S)*-epichlorohydrin or *(S)*-glycidol.

INTRODUCTION

We have previously reported the enzymatic resolution of 1,2-ketals of primary glycerol esters[1]. By varying the ketalizing ketone, the acyl group and the enzyme we obtained only relatively poor enantioselectivities. In another study we have used racemic secondary butanoates of 3-chloro-1,2-propanediol (1b and c) as substrates.[2]



1a-c



2a-d

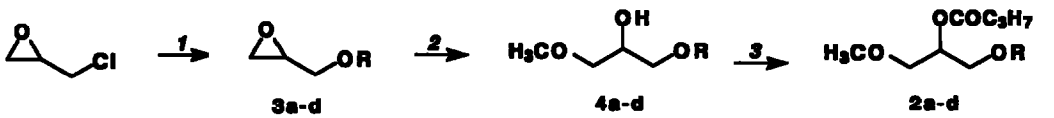
a) R = Ph, b) R = CH_2Ph, c) R = CH_2CH_2Ph, d) R = CH_2CH_2OPh

Hydrolysis of the butanoates **1b** and **c** was performed with five different lipases. Highest *E*-values was obtained with PPL ($E = 15$) and SAM-II ($E = 22$) for **1b** and **1c**, respectively. We now report the lipase catalysed hydrolysis of the 3-methoxy-1,2-propanediol derivatives **2a-d**. These C-3 compounds are potential building blocks for pseudolipids and derivatives of the anti-cancer drug $Et_{18}OCH_3$[3,4]. Other aspects of the present work was to study effects on the the enantioselectivities going through the series of derivatives **2a-d** and to compare the results with the results obtained for the corresponding chloro derivatives **1a**[5] and **1b** and **c**.

RESULTS AND DISCUSSION

The substrates **2a-d** were synthesised *via* the glycidyl ethers **3a-d**, which in turn were made from epichlorohydrin in a two-phase system consisting of aqueous sodium hydroxide, phase transfer catalyst and the appropriate alchohol[6]. Treatment of the glycidyl ethers with sodium methoxide in methanol afforded the secondary alcohols **4a-d**, which upon esterification with butanoic anhydride in pyridine gave the butanoates **2a-d** *(Scheme 1)*.

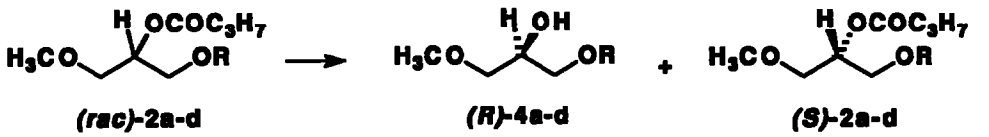
The homochiral glycidyl ethers *(R)*-**3b, c** and **d** were synthesised from *(S)*-epichlorohydrin[2], whereas *(R)*-**3a** was synthesised from *(S)*-glycidol, phenol and diethylazodicarboxylate (DEAD) in a Mitsunobu reaction[7]. Regioselective opening of the epoxides *(R)*-**3a-d** with sodium methoxide in methanol gave the alcohols *(R)*-**4a-d** in high enantiomeric excess *(ee)*.



3a-d **4a-d** **2a-d**

Scheme 1 **a)** R = Ph, **b)** R = CH_2Ph, **c)** R = CH_2CH_2Ph, **d)** R = CH_2CH_2OPh, *(1)* 50% w/v NaOH (aq), Bu_4NHSO_4 (cat) and MeOH; *(2)* MeOH, Na; *(3)* $(C_3H_7CO)_2O$, pyridine, DMAP (cat).

Lipase catalysed hydrolysis of the racemic butanoates **2a-d** afforded the corresponding *(R)*-alcohols in excess *(Scheme 2)*, whereas hydrolysis of the chloro compounds **1a, 1b** and **1c** gave the *(S)*-alcohols with the same enzymes[2,5]. The hydrolyses were performed in phosphate buffer (0.05 M) at constant pH (7.0) by titration with sodium hydroxide (0.1N). The conversion was monitored by pH-stat, but more accurate values for the conversion were obtained from $c = ee_s/ee_s + ee_p$[8]. The enantiomeric excess of the remaining esters *(S)*-**2a-d** and produced alcohols *(R)*-**4b, c** and **d** was determined by direct ananlysis on HPLC (Chiralcel-OB) without any further purification. Enantiomeric excess of the produced alcohol *(R)*-**4a** from hydrolysis of *(rac)*-**2a** was determined by analysis on achiral GLC stationary phase after derivatisation with *(S)*-phenylethyl isocyanate[9].



(rac)-2a-d *(R)*-4a-d *(S)*-2a-d

Scheme 2 a) R = Ph, b) R = CH_2Ph, c) R = CH_2CH_2Ph, d) R = CH_2CH_2OPh.
Lipases: PPL, PS, SAM-II, *Rhizomucor miehei* and *Candida antarctica* B.

The enantioselectivity *E* of the PPL catalysed hydrolysis of 2a increased from 6 to 12 as the reaction proceeded from 26 to 73% conversion *(Table 1)*. A similar increase was observed in the hydrolysis of 1b with the same enzyme[2]. This effect might be due to the fact that crude PPL consists of several enzymes which may possess different sterobias[10]. The most successful enzyme for resolution of 2a was lipase PS. Hydrolysis of racemic 2a with the *Candida antarctica* B lipase gave a conversion vs time curve (Figure 4a) which leveled off at approximately 50% conversion, suggesting that one enantiomer reacted considerably faster than the other. However, calculating the enantioselectivity during the reaction at seven different conversions gave *E* values ranging from below 10 to 80. This nonlinear relationship between the enantioselectivity *E* and the conversion, which is shown in figure 4b, does not accord with the general theory[8]. It must be emphasized that the immobilised *Candida antarctica* B lipase in contrast to PPL, is a pure enzyme, and the influence of other enzymes is believed to be minimal.

There are some previous reports that the enantioselectivity may be influenced by addition of cosolvent[11] or by changing solvent. In transesterifications catalysed by subtilisin, *E* may change from 3 to 61 when going from acetonitrile to dioxane[12]. The enantioselectivity in diglyceride hydrolysis has been influenced by changing the surface pressure.[13] For instance in the hydrolysis of 1,2-*rac*-dicaprin with lipoprotein lipase the enantioselectivity for the *sn*-1 position switched from 30 to 2 when the surface pressure was increased(calculated on the basis of given data). Moreover, addition of alkaloids has been reported to increase *E* from 1 to >100 in racemate resolutions using *Candida cylindracea* lipase.[14,15] Our observations of an increasing *E* as the reaction progressed has no parallel in the studies mentioned above. At the start of the reaction the *R*- and *S*-esters, in equal amounts, are the sole chemicals precent. As the reaction proceeds, their concentrations change at different rates. Furthermore, the *R*- and *S*-alcohols are formed also in unequal amounts. These changes in the reaction medium are the most likely causes for the observed increase in *E* during the reaction. For instance either the removal of the *R*-ester or the formation of the *R*-alcohol is the reason for the observed effect. It may be noted that the expression for *E* is based on Michaelis-Menton kinetics and absence of inhibitory effects.[8] We are presently investigating this matter.

Lipase	Conversion, %	React. time, h	ee_p	ee_s	E_p	E_s
Porcine pancreatic	26	0.6	67.0	23.2	6.4	6.1
	36	0.9	65.9	36.4	6.9	6.6
	73	4.1	36.9	>99	11.9	9.5
SAM II	21	6.8	71.8	19.0	7.3	7.2
Amano PS	54	17.5	84.0	>99	55.9	60.9
Rhizomucor miehei	17	18.5	28.7	6.0	1.9	1.9
Candida antarctica B	31	5.8	88.1	39.2	23.3*	21.5*

Table 1. Enzymatic hydrolysis of racemic butanoate **2a**. The conversion was calculated from $c = ee_s/ee_s + ee_p$. The *ee*-value of the remaining ester *(S)*-**2a** was measured by HPLC on Chiralcel OB, while the corresponding value for the produced alcohol *(R)*-**4a** was measured on a chiral GLC column after transformation into diastereomeric carbamates with *(S)*-phenylethyl isocyanate. E_p and E_s were calculated from ee_p and ee_s respectively. *E*-values marked with an asterix were extracted from seven independent measurements, which gave a non-linear plot of the enantioselectivity *(E)* vs. conversion (Figure 4b).

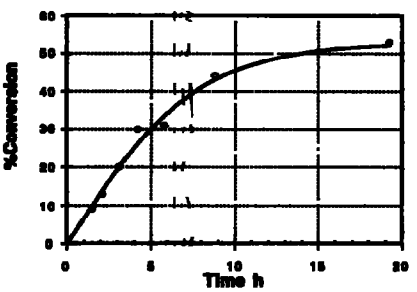


Figure 4a. Conversion vs time of the *Candida antarctica* catalysed hydrolysis of **2a**.

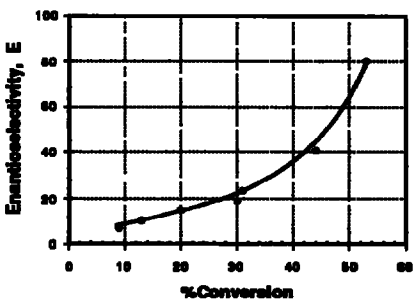


Figure 4b. Enantioselectivity, *E* (calculated from either ee_s or ee_p) vs % conversion for the same reaction as in figure 4a.

The hydrolyis of **2b**, **2c** and **2d** with the *Candida antartica* B lipase afforded the *(R)*-alcohols in large enantiomeric excess, with enantioselectivity values of 23, >100 and >55, respectively *(Tables 2, 3 and 4)*. Since the other lipases gave enantioselectivity values of ≤ 10, the usefulness of this novel enzyme is clearly demonstrated. It is also worth noticing that for the chloro series the *S*-alcohol was formed in excess in contrast to the corresponding methoxy derivatives. This different behaviour is not obvious on the basis of the recently clarified mechanism for lipase action.[16,17] Further studies with a broader range of substrates will be necessary.

Lipase	Conversion, %	React. time, h	ee_p	ee_s	E_p	E_s
Porcine pancreatic	33	0.9	49.9	24.5	3.8	3.8
	45	1.2	48.7	40.1	4.2	4.3
	59	1.7	44.9	63.7	4.9	4.8
	78	3.1	27.8	98.8	7.0	7.2
SAM II	32	20.5	20.7	9.6	1.7	1.7
Amano PS	91	2.3	7.0	71.8	1.9	2.0
Rhizomucor miehei	14	19.9	61.9	9.7	4.7	4.3
Candida antarctica B	20	10	89.5	21.8	22.5	18.1

Table 2. Enzymatic hydrolysis of racemic butanoate **2b**. The conversion was calculated from $c = ee_s/ee_s + ee_p$. The *ee*-value of the remaining ester *(S)*-**2b** and the produced alcohol *(R)*-**4b** were measured by HPLC on Chiralcel OB. E_p and E_s were calculated from ee_p and ee_s respectively.

Lipase	Conversion, %	React. time, h	ee_p	ee_s	E_p	E_s
Porcine pancreatic	66	1.4	26	50	2.7	2.6
SAM II	48	28	57	53	6.1	6.2
Amano PS	28	4	63	24	5.6	5.3
Rhizomucor miehei	50	25	<5	<5	1.2	1.2
Candida antarctica B	40	12.8	>99	65.3	>100	>100

Table 3 Enzymatic hydrolysis of racemic butanoate **2c**. The conversion was calculated from $c = ee_s/ee_s + ee_p$. The *ee*-value of the remaining ester *(S)*-**2c** and the produced alcohol *(R)*-**4c** were measured by HPLC on Chiralcel OB. E_p and E_s were calculated from ee_p and ee_s respectively.

Lipase	Conversion, %	React. time, h	ee_p	ee_s	E_p	E_s
Porcine pancreatic	36	4.0	5.7	3.2	1.1	1.1
SAM II	55	18.0	63.0	76.0	10.0	9.5
Amano PS	18	4.0	35.9	7.8	2.3	2.3
Rhizomucor miehei	8	20	65.6	5.7	5.1	5.1
Candida antarctica B	36	20	>94	52.8	>55	>55

Table 4. Enzymatic hydrolysis of racemic butanoate 2d. The conversion was calculated from $c = ee_s/(ee_s + ee_p)$. The *ee*-value of the remaining ester *(S)*-2d and the produced alcohol *(R)*-4d were measured by HPLC on Chiralcel OB. E_p and E_s were calculated from ee_p and ee_s respectively.

ACKNOWLEDGEMENTS

We are grateful to Dr Peter Eigtvedt, Novo-Nordisk, Bagsværd, Denmark for kind gifts of lipases from *Candida antarctica* and *Rhizomucor miehei*. We are also grateful to Dr K.Takami, Amano Enzyme Europe Ltd, Milton Keynes, UK. for kind gifts of lipases PS and SAM-II. The project has been supported by The Royal Norwegian Council for Scientific and Industrial Research, NTNF and Borregaard Fine Chemicals, Sarpsborg, Norway (to V. P.). Mr. Bjørn Olsrød, MS-laboratory, NTH, The University of Trondheim is thanked for MS measurements.

EXPERIMENTAL

Enzymes. The lipases Amano PS (*Pseudomonas cepacia*) and SAM-II (Pseudomonas sp.) were gifts from Amano Enzyme Europe Ltd, Milton Keynes, UK. The immobilised lipases from *Rhizomucor miehei* and *Candida antarctica* B were gifts from Novo-Nordisk A/S, Bagsværd, Denmark. PPL type II (Sigma L-3126) was purchased from Sigma.

Chemicals. (S)-Epichlorohydrin was purchased from Daiso Co., Ltd., Osaka, Japan (*ee* > 98%) and *(S)*-glycidol from Fluka.

Analytical methods. Enantiomeric excess *(ee)* of the alcohols (4b-d) and esters (2a-d) were determined by HPLC using a Varian 9000 system equipped with UV/VIS detector 2550 and a chiral column, Chiralcel OB, deliverd by J. T. Baker, Deventer, Holland. Solvents: 2a, hexane : isopropanol : ethanol = 98 : 1 : 1, 0.2 mL/min., 4b, hexane : ethanol = 90 : 10, 0.5 mL/min., 2b, hexane : ethanol = 97 : 3, 0.15 mL/min., 4c, hexane : ethanol = 95 : 5, 0.2 mL/min., 2c, hexane : isopropanol = 90 : 10, 0.25 mL/min., 2d and 4d, hexane : isopropanol = 96 : 4, 0.5 mL/min. Optical rotations were determined using Optical Activity Ltd. AA-10 Automatic polarimeter, concentrations (c) are given in g/100mL. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using TMS as internal reference, shift values are in ppm. The instrument was JEOL EX-400 operating at 400 MHz for ^1H and 100.4 MHz for ^{13}C. All asignements are confirmed by ^1H-^{13}C

correlation and DEPT. Mass spectral measurements were performed using an AEI MS-902 instrument.

Distillations were performed in the "bulb to bulb" manner using Büchi GKR-50 equipement except for **3a**, **3c** and **4a**.

General experimental procedure for enzymatic hydrolysis. The butanoates **2a-d** (1 mmol) were suspended in 0.05M phosphate buffer (70 mL, pH 7.0). The lipases PPL (110 mg), SAM-II (20 mg), PS (150 mg), Mucor lipase (60 mg) and Candida lipase (30 mg) were added and the reaction mixture stirred at room temp. The enzymatic hydrolysis was monitored by a pH-stat consisting of a Radiometer PHM 64 pH meter and a Metrohm Herisau Dosimat pump. Addition of 0.1N NaOH solution was controlled by a Copam PC. The hydrolysis was stopped by repeated extraction with Et_2O and the reaction mixture was analysed directly by the above mentioned methods.

*Preparation of glycidyl ethers (rac)- **3a-d**, general procedures.* Epichlorohydrin (104.56g 1.13 mol) was added dropwise to a mixture of 50% aqueous NaOH (150 mL) and Bu_4NHSO_4 (2.98 g). The final solution was stirred vigorously at room temp for 2h and then the alcohol (0.213 mol) was added in portions over 1h. The temperature was kept at 30 °C by sufficient cooling on ice/water throughout both additions. The mixture was stirred over night at room temp and then 300 mL of water was added, extraction with Et_2O (4x150 mL), drying over $MgSO_4$ and bulb to bulb vacuum distillation gave the title compounds.

Phenyl glycidyl ether (rac)-**3a**, $bp_{0.3}$: 62-64 °C, 51 %, ^1H NMR: 2.76, 2.91, 3.36 (oxirane), J_{gem}= 4.8 Hz, J_{vic}= 4.8 and 2.6 Hz, 3.96, 4.21, (CH_2), J_{gem}= 11.0 Hz, J_{vic}= 3.3 and 5.5 Hz. ^{13}C NMR: 44.8 (t) and 50.7 (d) (oxirane), 68.7 (t), 114.6 (2d), 121.2 (d), 129.5 (2d) and 158.5 (s).

Phenylmethyl glycidyl ether (rac)-**3b**, $bp_{0.1}$: 130 °C, 80%, ^1H NMR: 2.62, 2.80, 3.19 (oxirane), J_{gem}= 4.5 Hz, J_{vic}= 4.5 and 3.6 Hz, 3.43, 3.77, (CH_2) J_{gem}= 11.2 Hz, J_{vic}= 3.1 and 5.7 Hz, ν_{Bn} = 4.56 and 4.61, J_{AB} = 11.5 Hz. ^{13}C NMR 44.3(t) and 50.9(d) (oxirane), 70.8(t), 73.3(t), 127.4(d), 127.8(2d), 128.4(2d) and 137.9(s)

Phenylethyl glycidyl ether (rac)-**3c**, $bp_{0.6}$: 106-108 °C, 78%, ^1H NMR: 2.59, 2.78, 3.13 (oxirane), J_{gem}= 4.5 Hz, J_{vic}= 4.5 and 3.6 Hz, 3.40, 3.73 , (CH_2), J_{gem}= 11.2 Hz, J_{vic}= 3.1 and 5.7 Hz, ABX_2-syst for -OCH_2CH_2- 3.69 (1H), 3.74 (1H) and 2.90 (2H), J_{AB} = 7.4 Hz, J_{AX} = 5.5 Hz, and J_{BX} = 5.8 Hz. ^{13}C NMR: 44.3(t) and 50.9(d) (oxirane), 36.3(t), 71.5(t), 72.4(t), 126.2(d), 128.4(2d), 128.9(2d) and 138.7(s).

*Phenoxyethyl glycidyl ether (rac-**3d**)*: $bp_{0.5}$: 185-190 °C, 71%, ^1H NMR: 2.63, 2.80 and 3.19 (oxirane), J_{gem}= 4.4 Hz, J_{vic}= 4.4 and 2.8 Hz, 3.49, 3.87, (CH_2), J_{gem}= 12.0 Hz, J_{vic}= 2.8 and 6.0 Hz, ABX_2-syst. for -OCH_2CH_2OPh 3.84 (1H), 3.91(1H) and 4.13 (2H) J_{AB} = 11.0 Hz J_{AX} = 4.8 and J_{BX} = 5.2.

^{13}C NMR: 44.3 (t) and 50.7 (d) (oxirane), 67.3 (t), 69.9 (t), 72.1 (t), 114.6 (2d), 120.6 (d), 129.4 (2d) and 158.7 (s). $M^{\cdot+}$ calc. for $C_{11}H_{14}O_3$ 194.0943, found 194.0946.

(R)-(-)-Phenyl glycidyl ether, (R)-**3a**. Phenol (0.631g 6.7 mmol), triphenylphosphine (1.76g, 6.7 mmol) and *(S)*-glycidol (0.496g 6.7 mmol) were mixed in THF (50 mL) at room temp and diethyl azodicarboxylate (6.7 mmol) was added. The mixture was stirred at room temp for 4h and the solvent was removed at reduced pressure. The residue was dissolved in hexane : EtOAc 4:1, and the suspension was filtered. The filtrate was concentrated and distillation gave *(R)*-**3a**, $bp_{0.8}$: 110 °C, 31%, $[\alpha]_D^{20}$ = - 12.4 (c 2.49 EtOH).

R)-(-)-Phenylmethyl glycidyl ether (R)-**3b** and *(R)-(-)-2-Phenyletyl glycidyl ether (R)*-**3c** were prepared as previously described[2].

(R)-(-)-Phenoxyethyl glycidyl ether (R)-**3d** was prepared as *(R)*-**3b** and *(R)*-**3c** from *(S)*-epichlorohydrin: $bp_{0.8}$: 185-190 °C, 70%, $[\alpha]_D^{20}$ = - 11.0 (c 2.14 EtOH).

Preparation of alcohols (rac)- **4a-d** *from epoxides (rac)*-**3a-d**,*general procedures*, To a solution of Na (2.55g 0.111 mol) in abs. MeOH (100 mL) at room temp was added the epoxide (0.1 mol) during 30 min. The reaction was continued for further 3h. at 40 °C. Evaporation of the MeOH at reduced pressure, addition of Et_2O (150 mL), extraction with H_2O, drying over $MgSO_4$ and vacuum distillation afforded the title compounds.

1-Phenyl-3-methoxy-1,2-propanediol (rac)-**4a**) and *(R)*-**4a**, $bp_{0.2}$: 96-100 °C, 76%, ^1H NMR ABMXY-syst. for $-CH_2CH(OH)CH_2OCH_3$, 4.01 (1H), 4.03 (1H), 4.17 (1H), 3.54 (1H) and 3.59 (1H) J_{AB} = 10.2, J_{AM} = 6.2, J_{BM} = 4.8, J_{XY} = 9.9, J_{XM} = 6.1 and J_{YM} = 4.4, 3.41 (3H, $-OCH_3$) and 2.67 (1H-br, -OH) ^{13}C NMR 59.3 (q), 68.9(t), 69.1 (d), 73.5 (t), 114.6 (2d), 121.1 (d), 129.5 (2d) and 158.5 (s). *(R)*-**4a** was synthesised in the same manner from *(R)*-**3a**, $[\alpha]_D^{20}$ = +2.6 (c 0.76 EtOH), 90.1% *ee* (GLC of carbamate derivative)] $M^{\cdot+}$ calc for $C_{10}H_{14}O_3$ 182.0943, found 194.0945.

1-Phenylmethyl-3-methoxy-1,2-propanediol [*(rac)*-**4b** and *(R)*-**4b**]: $bp_{1.0}$: 150 °C, 86%, ^1H NMR: 4.57 (2H, $-OCH_2Ph$), ABMXY-syst for $-CH_2CH(OH)CH_2OCH_3$, 3.43 (1H), 3.48 (1H), 4.01 (1H), 3.50 (1H) and 3.55 (1H) J_{AB} = 10.1, J_{AM} = 6.2, J_{BM} = 4.5, J_{XY} = 9.5, J_{XM} = 6.4 and J_{YM} = 5.6, 3.39 (3H, $-OCH_3$) and 2.45 (1H-br, -OH). ^{13}C NMR: 59.2(q), 69.4(d), 71.3(t), 73.5 (t), 73.8 (t), 127.7 (2d), 127.7 (d), 129.0 (2d) and 138.0 (s). *(R)*-**4b** was synthesised in the same manner from *(R)*-**3b**, $[\alpha]_D^{20}$ = +4.2 (c 1.67 MeOH) >98% ee (HPLC).$M^{\cdot+}$ calc. for $C_{11}H_{16}O_3$ 196.1099, found 196.1104.

1-Phenylethyl-3-methoxy-1,2-propanediol (rac)-**4c** and *(R)*-**4c**, $bp_{1.0}$: 170 °C, 90%, ^1H NMR: ABX_2 -syst for $-OCH_2CH_2Ph$ 3.67 (1H), 3.70 (1H) and 2.89 (2H) J_{AB} = 9.5, J_{AX} = 7.2 and J_{BX} = 6.8 ABMXY-syst for $-CH_2CH(OH)CH_2OCH_3$, 3.37 (1H), 3.41 (1H), 3.92 (1H), 3.45 (1H) and 3.51 (1H) J_{AB} = 9.9, J_{AM} = 3.3, J_{BM} = 4.4, J_{XY} = 9.9, J_{XM} = 6.6 and J_{YM} = 4.4, 3.36 (3H, $-OCH_3$) and 2.56 (1H-br, -OH) ^{13}C

NMR: 36.2(t), 59.2(q), 69.3(d), 71.9(t), 72.3 (t), 73.7 (t), 126.5 (d), 128.4 (2d), 128.9 (2d) and 138.8 (s). *(R)*-4c was synthesised in the same manner from *(R)*-3c, $[\alpha]_D^{20}$ = +5.6 (c 1.07 MeOH), $[\alpha]_D^{20}$ = +1.0 (c 1.06 Benzen), >98% *ee* (HPLC), $[M\text{-}Bn]^+$ calc for $C_5H_{11}O_3$ 119.0708, found 119.0709.

1-Phenoxyethyl-3-methoxy-1,2-propanediol (rac)-4d and *(R)*-4d, $bp_{1.0}$: 200 °C, 70%, ^1H NMR: A_2X_2 -syst. for -OCH_2CH_2OPh 3.86 (2H) and 4.13 (2H) J_{AX} = 4.4, ABMXY-syst. for -CH_2-CH(OH)-CH_2-OCH_3, 3.43 (1H), 3.46 (1H), 3.99 (1H), 3.57 (1H) and 3.64 (1H) J_{AB} = 10.0, J_{AM} = 6.4, J_{BM} = 4.4, J_{XY} = 10.0, J_{MX} = 6.4 and J_{MY} = 4.4, 3.38 (3H, OCH_3) and 2.66 (1H-br, -OH) ^{13}C NMR: 59.2(q), 67.2(t), 69.4(d), 70.0(t), 72.6(t), 73.6(t), 114.6(2d), 121.0(d), 129.5(2d) and 158.6(s) *(R)*-4d was synthesised in the same manner from *(R)*-3d, $[\alpha]_D^{20}$ = +1.5 (c 2.01 EtOH, 91% *ee* (HPLC) $M^{\cdot+}$ calc. for $C_{12}H_{18}O_4$ 226.1205, found 226.1210.

Preparation of esters (rac-2a-d) from alcohols (rac-4a-d), general procedure: The alcohol (0.055 mol) was stirred at room temp with butanoic anhydrid (0.082 mol) in dry pyridine (50 mL) and 4-dimethylaminopyridine (DMAP) as catalyst. Evaporation of the pyridine at reduced pressure, addition of Et_2O (200 mL), extraction with 2% HCl (4x50 mL), drying over $MgSO_4$ and vacuum distillation gave the title compounds.

2-Butanoyl-1-phenyl-3-methoxy-1,2-propanediol (rac)-2a, $bp_{1.0}$: 200 °C, 85%, ^1H NMR: ABMXY-syst for -$CH_2CH(OR)CH_2OCH_3$, 4.12 (1H), 4.15 (1H), 5.33 (1H), 3.64 (1H) and 3.67 (1H) J_{AB} = 10.0, J_{AM} = 5.6, J_{BM} = 4.8, J_{XY} = 10.5, J_{MX} = 4.5 and J_{MY} = 5.0, 3.39 (3H, OCH_3), R = $CH_3CH_2CH_2CO$, 0.95, 1.67, 2.34 ^{13}C NMR: 13.6(q), 18.2(t), 36.2(t), 59.3(q), 66.3(t), 70.6(d), 71.0(t), 114.5(2d), 121.1(d), 129.5(2d), 158.6(s) and 173.2(s), $M^{\cdot+}$ calc. for $C_{14}H_{20}O_4$ 252.1362, found 252.1364.

2-Butanoyl-1-phenylmethyl-3-methoxy-1,2-propanediol (rac)-2b, $bp_{1.0}$: 220 °C, 80%, ^1H NMR: AB-syst for -OCH_2Ph 4.53 (1H) and 4.56 (1H) J_{AB} = 11.5, ABMXY-syst for -$CH_2CH(OR)CH_2OCH_3$, 3.55 (1H), 3.57 (1H), 5.20(1H), 3.61 (1H) and 3.63 (1H) J_{AB} = 11.0, J_{AM} = 5.6, J_{BM} = 4.2, J_{XY} = 11.2, J_{XM} = 5.6 and J_{MY} = 5.6, 3.35 (3H, -OCH_3), R = $CH_3CH_2CH_2CO$ 0.95, 1.66, 2.32. ^{13}C NMR: 13.6(q), 18.5(t), 36.3(t), 59.2(q), 68.7(t), 71.1(d), 71.3(t), 73.2(t), 127.6(2d), 127.7(d), 128.4(2d), 138.0(s) and 173.2(s), $[M - COC_3H_7]^+$ calc. for $C_{10}H_{15}O_3$ 195.1021, found 195.1024.

2-Butanoyl-1-phenylethyl-3-methoxy-1,2-propanediol (rac)-2c, $bp_{1.0}$: 230 °C, 83%, ^1H NMR: ABX_2 syst for -OCH_2CH_2Ph 3.62 (1H), 3.69 (1H) and 2.86 (2H) J_{AB} = 9.3, J_{AX} = 6.8 and J_{BX} = 6.8, ABMXY-syst. for -$CH_2CH(OR)CH_2OCH_3$, 3.48(1H), 3.51 (1H), 5.13 (1H), 3.57 (1H) and 3.59 (1H) J_{AB} = 9.5, J_{AM} = 6.3, J_{BM} = 5.5, J_{XY} = 10.7, J_{XM} = 5.4 and J_{YM} = 4.9, 3.33 (3H) -OCH_3, R = $CH_3CH_2CH_2CO$ 0.94, 1.65, 2.31, ^{13}C NMR: 13.6(q), 18.5(t), 36.2(t), 36.3(t), 59.2(q), 69.2(t), 71.0(d), 71.3(t), 72.3(t), 126.2(d), 128.3(2d), 128.9(2d), 138.9 (s) and 173.2(s), $[M\text{-}Bn]^+$ calc for $C_9H_{17}O_4$ 189.1127, found 189.1129.

2-Butanoyl-1-phenoxymethyl-3-methoxy-1,2-propanediol (rac)-2d, $bp_{1.0}$: 240 °C, 83%, ^1H NMR: ABX_2 syst for $-OCH_2CH_2OPh$ 3.82 (1H), 3.86 (1H) and 4.10 (2H) J_{AB} = 11.3, J_{AX} = 5.3 and J_{BX} = 4.8, ABMXY-syst. for $-CH_2CH(OR)CH_2OCH_3$, 3.54 (1H), 3.56 (1H), 5.18 (1H), 3.70 (1H) and 3.72 (1H) J_{AB} = 13.0, J_{AM} = 4.8, J_{BM} = 4.8, J_{XY} = 10.5, J_{MX} = 5.7 and J_{MY} = 4.8, 3.35 (3H) $-OCH_3$, R = $CH_3CH_2CH_2CO$ 0.94, 1.65, 2.32. ^{13}C NMR: 13.5(q), 18.5(t), 36.3(t), 59.2(q), 67.2(t), 69.8(t), 69.9(t), 71.0(d), 71.2(t) 114.6(2d), 120.9(d), 129.4(2d), 158.7(s) and 173.2(s), $M^{\cdot+}$ calc for $C_{16}H_{24}O_5$ 296.1624, found 296.1625.

REFERENCES

1. Partali, V.; Melbye, A. G.; Alvik, T.; Anthonsen, T. *Tetrahedron: Asymmetry*, 1992, *3*, 65-72.
2. Partali, V.; Waagen, V.; Alvik, T.; Anthonsen, T. *Tetrahedron: Asymmetry*, 1993, *4*, 961-968.
3. Eibl, H. *Angew. Chem. Int. Ed. Engl.*, 1984, *23*, 257-328.
4. Berdel, W. E. *J. Am. Oil Chem. Soc.*, 1988, *65*, 1877-1880.
5. Ader, U.; Schneider, M. P. *Tetrahedron: Asymetry*, 1992, *3*, 201-204 and 205-208.
6. Mouzin, G.; Cousse, H.; Rieu, J. -P.; Duflos, A. *Synthesis*, 1983, 117-119.
7. Mitsunobu, O. *Synthesis*, 1981, 1-28.
8. Sih, C. J.; Wu, S.-H. *Topics in Stereochemistry*, 1990, *19*, 63-125.
9. Sonnet, P. E.; Piotrowski, E. G.; Boswell, R. T. *J. Chromatogr.*, 1988, *436*, 205-217.
10. Faber, K. (1992) *Biotransformations in organic chemistry*, Springer-Verlag, 1992, p. 81-82.
11. Boutelje, J.; Hjalmarsson, M.; Hult, K.; Lindbäck, M.; Norin, T. *Bioorg.Chem.*, 1988, *16*, 364 - 375.
12. Fitzpatrick, P. A.; Klibanov, A. M. *J. Am. Chem. Soc.*, 1991, *113*, 3166 - 3171.
13. Rogalska, E.; Ransac, S.; Verger, R. *J. Biol. Chem.*, 1993, *268*, 792-794.
14. Itoh, T.; Ohira, E.; Takagi, Y.; Nishiyama, S.; Nakamura, K. Bull. Chem. Soc Jpn., 1991, *64*, 624-7.
15. Guo, Z.-W.; Sih, C. J., *J. Am. Chem. Soc.*, 1989, *111*, 6836 - 6841.
16. Rogalska, E.; Cudrey, C.; Ferrato, F.; Verger, R. *Chirality*, 1993, *5*, 24-30.
17. van Tilbeurgh, H.; Egloff, M.-P.; Martinez, C.; Rugani, N.; Verger, R.; Cambilleau, C., *Nature*, 1993, *362*, 814-820.