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STUDIES ON THE ENANTIOSELECTIVITY OF THE TRANSESTERIFICATION OF 2-METHYL-1,4-BUTANEDIOL AND ITS DERIVATIVES CATALYZED BY *Pseudomonas fluorescens* LIPASE IN ORGANIC SOLVENTS

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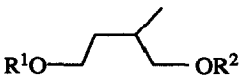
Abstract. - The irreversible transesterification of 2-methyl-1,4-butanediol **1a** and its benzyl ethers **2a** and **3a** catalyzed by *Pseudomonas fluorescens* lipase in chloroform was studied, the highest ee (>98%) having been obtained for the 4-benzyl ether **2a**.

Introduction

The enzymatic transesterification of racemic and prochiral alcohols can proceed with excellent enantioselectivity and has been widely used in organic synthesis, when the preparation of optically pure chiral synthons is desired.[1] A recent procedure prevents limiting back reactions, relying on enol esters as irreversible acyl donors and a lipase[2,3] as the biocatalyst.[4] We have shown that, using the lipase from *Pseudomonas fluorescens* (PFL)[5] in chloroform or dichloromethane, the above reaction is highly enantioselective on a variety of 2-methyl alkanols[6] and can be also efficiently applied to the prochiral 2-methyl-1,3-propanediol[7] and its racemic monoderivatives.[8] A logical extension of the previous work was to examine 2-methyl-1,4-butanediol **1a** and its derivatives as substrates for the PFL-catalyzed transesterification.

PFL-Catalyzed Transesterification of 2-Methyl-1,4-butanediol 1a

We investigated the enantioselectivity of the PFL-catalyzed transesterification in an organic solvent using the diol **1a** as substrate, taking into account that, according to our previous experience,[6-8] the maximum enantiomeric excess (ee) for α-methyl substituted primary alcohols could be obtained if the reaction was carried out towards a 60% conversion to the corresponding acetate.[9] The nearly optically pure acetate might be available if the transacetylation was stopped when 60% alcohol was still present.



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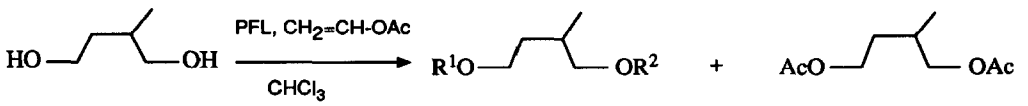
a. $R^1=R^2=H$ **b.** $R^1=H$; $R^2=Ac$
c. $R^1=Ac$; $R^2=H$ **d.** $R^1=R^2=Ac$

A few experiments were carried out at different conversion of the diol **1a** to the monoacetates **1b** and **1c** or to the diacetate **1d**.[10] When 34% of the unreacted diol **1a** was present (4 h), 15% of the racemic diacetate **1d** and 50% of the mixture of the monoacetates **1b** and **1c** (7:3 ratio, as established by 500 MHz ^{1}H-NMR) were formed. In this case, the (R)-(+)-diol **1a** was isolated with 70% ee, as established by its optical rotation.[11] The two regioisomeric monoacetates, *i.e.*, 1- and 4-acetate **1b** and **1c** could not be separated by column chromatography and at this stage were not further investigated.



1a **1b** $R^1=H, R^2=Ac$ **1c** $R^1=Ac, R^2=H$ **1d**

Scheme 1

In another experiment at longer times (24 h), all the diol **1a** reacted and 60% of the racemic diacetate **1d** and 40% of the mixture of monoacetates **1b** and **1c** (7:3 ratio by capillary GLC) were formed. In this case, the hydrolysis of the above mixture of monoacetates to the diol **1a** was conveniently performed with $LiAlH_4$.[12] The (R)-(+)-diol **1a** was isolated (20% ee) and the low enantioselectivity of the reaction could be explained in different ways. We therefore decided to investigate in more details the reaction at the single hydroxy groups of the diol **1a**.

PFL-Catalyzed Transesterification of 2-Methyl-1,4-butanediol, 4-Benzyl Ether 2a

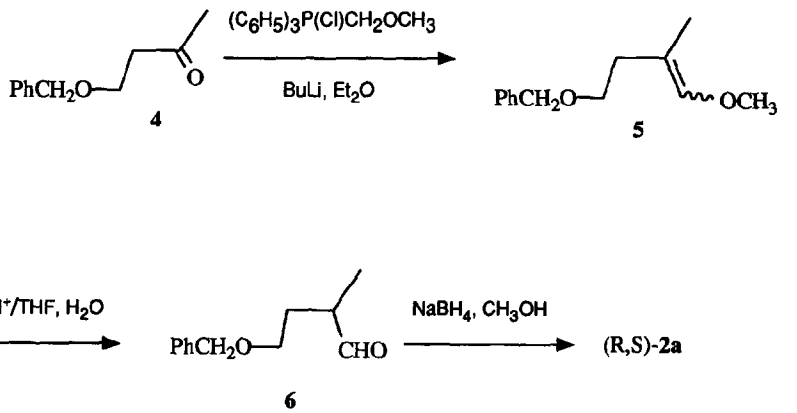
Among the possible derivatives of 2-methyl-1,4-butanediol **1a**, we chose the benzyl ethers **2a** and **3a**, anticipating that, due to the relative positions of the stereogenic center and the hydroxyl group, the enantioselectivity of the two enzymatic reactions could be different. In fact, the 4-benzyl ether **2a** can be regarded as a primary alcohol which presents a methyl group located at the α-position and a benzyloxy

moiety at the γ-carbon. The PFL-catalyzed transesterification, therefore, should not differ too much from other similar substrates.[6] In the 1-benzyl ether **3a**, the alcoholic function is more distant from the

2 **3**

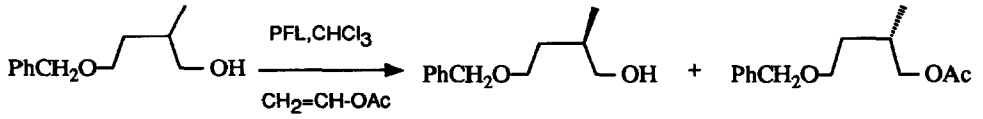
a. R=H **b.** R=$COCH_3$

stereogenic center and a lower enantioselectivity could be expected, as we already noticed for other similar compounds.[13] It should also be mentioned that both monoethers, if optically pure, can be valuable chiral synthons, as already shown for the compound **2a**.[14] For the preparation of the racemic benzyl ether **2a**, among a few synthetic routes attempted, the method outlined in the Scheme 2 was chosen because offered the most reproducible yields (60% overall).



Scheme 2

Commercially available 4-benzyloxy-2-butanone **4** was the starting material and a Wittig condensation with methoxymethyltriphenylphosphonium chloride[15] afforded the enol ether **5** (undefined E/Z mixture). This compound was hydrolyzed to the aldehyde **6**, which was then reduced ($NaBH_4$/MeOH) to the required racemic 4-benzyl ether **2a**. The PFL-catalyzed transacetylation in chloroform (Scheme 3) afforded in two separate incubations, the (+)-alcohol **2a** and the (+)-acetate **2b** (38-40% yield), both with a high ee (98% and 85%, respectively).



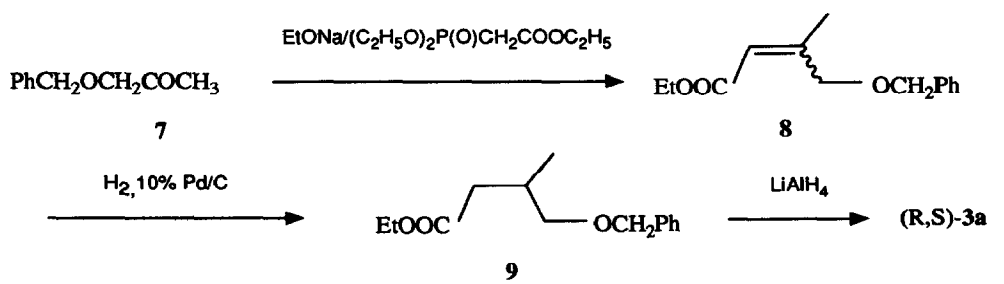
(R,S)-**2a** (R)-**2a** (S)-**2b**

Scheme 3

The configuration of (+)-**2a** was established as *R* by comparison of its optical rotation with the literature value.[14] The extent of the ee was established by comparison of the 500 MHz ^{1}H-NMR spectra of the MTPA esters prepared from racemic and (+)-**2a** and (S)-(-)-MTPA chloride.[16] For the optical purity and configuration of the (+)-acetate **2b**, the hydrolysis with $LiAlH_4$ afforded (S)-(-)-**2a** (85% ee as determined *via* its MTPA ester). The stereochemical outcome of the enzymatic reaction clearly showed that the 4-benzyl ether **2a** behaves as the other primary alcohols bearing the methyl group at the α-position.[6]

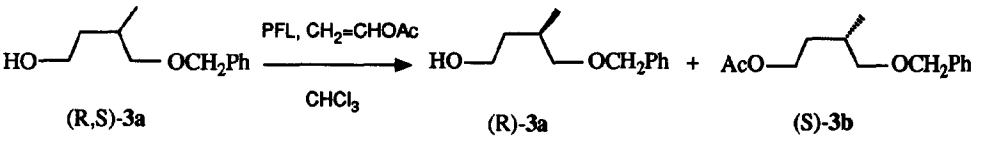
PFL-Catalyzed Transesterification of 2-Methyl-1,4-butanediol, 1-Benzyl Ether 3a

For the preparation of the racemic 1-benzyl ether **3a**, the starting material, 1-benzyloxy acetone **7**, was prepared from propargyl alcohol according to a published procedure.[17] A Wittig-Hörner condensation[18] of **7** with triethyl phosphonoacetate afforded the unsaturated ester **8** (undetermined E/Z ratio). The compound **8** was hydrogenated to the saturated ester **9**, which on $LiAlH_4$ reduction afforded the required racemic monoether **3a** in 43% overall yields (Scheme 4).



Scheme 4

The PFL-catalyzed resolution of the racemic **3a** was carried out in chloroform in the usual manner (Scheme 5) and, in two separate sets of incubations, the (-)-alcohol **3a** and the (-)-acetate **3b** were obtained in 38 and 40% yield, respectively. The extent of ee for (-)-**3a** was established as 40% by the 500 MHz ^{1}H-NMR spectra of the MTPA esters prepared from racemic and (-)- **3a** and (S)-(-)-MTPA chloride.[16]



Scheme 5

The configuration of (-)-**3a** was established as *R* by hydrogenolysis of the benzyl group, which afforded the (R)-(+)-diol **1a**.[11] For the assessment of the configuration and optical purity (52% ee) of the enzymatically prepared (-)-acetate **3b**, we compared the optical rotation of this sample, $[\alpha]_D$ -1.3, with that of the acetate prepared by acetylation of 40% ee (R)-(-)-**3a**. This acetate (R)-**3b** exhibited a positive optical rotation, $[\alpha]_D$ +1, and therefore an *S* configuration was established for the enzymatically formed (-)-acetate **3b**.

Conclusions

We have found that the PFL-catalyzed transesterification of 2-methyl-1,4-butanediol **1a** can be used to prepare 70% ee (R)-(+)-diol **1a**. This can be regarded as a satisfactory result, considering that the substrate contains two primary alcohol functions, differently located with respect to the stereogenic center. The benzyl ethers **2a** and **3a** behave differently in the enzymatic reaction. In fact, the 4-benzyl ether **2a**, in which the stereogenic center is α to the alcoholic group to be enzymatically esterified, is enantioselectively resolved into the (R)-(+)-alcohol **2a** and the (S)-(+)-acetate **2b** (98 and 85% ee, respectively). The 1-benzyl ether **3a** was resolved with a lower enantioselectivity (38-40% ee), thus confirming that when the stereogenic center is far from the reacting group, the stereochemical discrimination of the two enantiomers is less efficient. All these informations, together with the results obtained by us for other similar substrates, furnish interesting indications on the possible topology of the active site of the lipase in organic solvents. Although more results from other structurally related compounds are desirable, we have already suggested a simple model which explains the stereochemical requirements for the transesterification of 2-substituted alkanols.[19]

Experimental Section.

Pseudomonas fluorescens lipase and all the chemicals were purchased from Fluka (Switzerland). The enzyme was used without further purification. Infrared spectra were recorded on a 1420 Perkin Elmer spectrometer (1% solutions in chloroform). Unless otherwise indicated, ^{1}H-NMR are referred to 60 MHz spectra, recorded on a Varian EM 360 L spectrometer for solution in $CDCl_3$, using $SiMe_4$ as internal standard. The 500-MHz ^{1}H-NMR spectra were recorded on a Bruker AM-500 spectrometer. GLC analyses were performed on a Hewlett Packard gaschromatograph (Mod. 5890/II) equipped with a fused silica capillary column (HP-5). MS analyses were carried out on a Hewlett Packard instrument (Mod. 5988) by direct inlet probe and electronic impact techniques (electron energy at 70 eV and ion source at 270 °C). Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Distillations for analytical purposes were accomplished using a glass tube oven Büchi GKR-50. TLC analyses were performed on silica gel Merck 60 F254 plates and column chromatographies carried out on silica gel Merck 60 (230-400 mesh). As a general procedure, after extraction of the products in a given solvent, the organic solutions were dried on sodium sulfate, the solvent removed at reduced pressure and the mixture of products purified as described.

2-Methyl-1,4-butanediol 1a

To a suspension of $LiAlH_4$ (5.74 g, 0.151 mol) in dry THF (230 mL), a solution of diethyl 2-methyl succinate (5 g, 26.6 mmol) in THF (15 mL) was added and the mixture was refluxed (3 h). Addition of water (5.74 mL), 15% NaOH (5.74 mL) and water (17.22 mL) was followed by filtration onto Celite and evaporation of the solvent afforded a residue which was purified by distillation (95 °C at 0.04 mm Hg) to give pure **1a** (2.2 g, 79 %); δ_H 0.95 (d, 3 H, J = 6 Hz, *CH*$_3$CH), 1.5 - 1.65 (m, 2 H, *CH*$_2$-CH$_2$OH), 1.7 - 1.8 (m, 1 H, *CH*), 3.4 - 3.8 (m, 4 H, *CH*$_2$OH), 4.6 (m, 2 H, exchangeable); ν_{max}/cm^{-1} 3360;. MS: 86 [M-18]$^+$, 71 [M-33]$^+$. $C_5H_{12}O_2$: Anal. found: C, 57.64; H, 11.58; Calc.: C, 57.69; H, 11.54%.

2-Methyl-1,4-butanediol, 4-Benzyl Ether 2a

The compound was prepared in three steps from commercial 4-benzyloxy-2-butanone **4**.

(a) To a suspension of methoxymethyltriphenylphosphonium chloride (4.615 g, 13.46 mmol) vigorously stirred at -20°C under nitrogen, in anhydrous diethyl ether (40 mL), a solution of n-BuLi (10 mL, 1.6 M in hexane) was added. After 20 min a solution of the ketone **4** (2 g, 11.22 mmol) in diethyl ether (10 mL) was added and the reaction mixture was stirred at -20 °C for 2 h, then at room temperature for 3 h. 1N HCl was added to neutrality and the products were extracted with diethyl ether (3 x 30 mL). After work-up, the residue (4 g) was purified by column chromatography and the elution with hexane/ethyl acetate (9:1) afforded pure methoxy enolether **5** (2.06 g, 89%). The compound **5** was used without further purification for the next step. δ_H 1.6 (s, 3 H, *CH*$_3$C=), 2.0 - 2.6 (m, 2 H, *CH*$_2$-C=), 3.35 - 3.75 (m, 2 H, CH$_2$-*CH*$_2$-O), 3.55 (s, 3 H, *CH*$_3$-O), 4.6 (s, 2 H, *CH*$_2$Ph), 5.9 (s, 1 H, *CH*=), 7.4 (s, 5 H, aromatic).

(b) The aldehyde **6** was prepared by acidic hydrolysis of the previous compound **5**. Thus, a solution of the enol ether **5** (2.06 g) in THF (50 mL) was treated with 0.1 M H_2SO_4 (25 mL) and the solution refluxed (12 h). The reaction was neutralized with sodium hydrogen carbonate, the solvent evaporated at reduced pressure and the products extracted with diethyl ether (3x30 mL). After work-up, the residue of the aldehyde (1.75 g) was used without further purification. An analytical sample was obtained by distillation: b.p. 73-76 °C (0.03 mm Hg); δ_H 1.1 (d, 3 H, J = 7 Hz, *CH*$_3$-CH), 1.4 - 2.9 (m, 3 H, *CH*$_2$-*CH*), 3.6 (t, 2 H, J = 6 Hz, CH$_2$-*CH*$_2$O), 4.45 (s, 2 H, *CH*$_2$Ph), 7.4 (s, 5 H, aromatic), 9.9 (s, 1 H, CHO); ν_{max}/cm^{-1} (neat) 1725.

(c) The (R,S)-monoprotected diol **2a** was prepared by $NaBH_4$ reduction (0.35 g, 9.5 mmol) of the aldehyde **6** (1.2 g, 6.25 mmol) in methanol (25 mL). The reaction was stirred at room temperature for 1 h, then a conventional work-up afforded pure **2a** (0.921 g, 76%); b.p. 68-70 °C at 0.03 mm Hg; δ_H 0.9 (d, 3 H, *CH*$_3$-CH), 1.2 (m, 3 H, *CH*$_2$-*CH*), 2.9 (m, 1 H, exchangeable), 3.45 - 3.9 (m, 4 H, *CH*$_2$OH, *CH*$_2$OCH$_2$Ph),

4.65 (s, 2 H, CH_2Ph), 7.4 (s, 5 H, aromatic); ν_{max}/cm^{-1} 3350; MS 194 $[M]^+$, 176 $[M-18]^+$, 161 $[M-33]^+$, 107 $[M-87]^+$, 91 $[M-103]^+$. $C_{12}H_{18}O_2$: Anal. found: C, 74.35; H, 9.4. Calc.: C, 74.2; H, 9.28%.

2-Methyl-1,4-butanediol, 1-Benzyl Ether 3a

(a) Sodium (0.89 g, 38.7 mmol) was dissolved under stirring, at room temperature, in absolute ethanol (20 mL). After cooling at 0 °C, a solution of triethyl phosphonoacetate (6.88 g, 30.7 mmol) in ethanol (8 mL) was added. The reaction was kept under stirring at 0 °C for 20 min and then 1-benzyloxy acetone **7** (prepared according to Ref. 17) (5.036 g, 30.7 mmol) in ethanol (12 mL) was added. The reaction was stirred at room temperature for 8 h, then neutralized with HCl 1N and ethanol was evaporated under vacuum. The reaction mixture was extracted with dichloromethane (3 x 50 mL) and the usual work-up afforded a residue (6.2 g) which was purified by column chromatography. The elution with hexane/ethyl acetate (9:1) afforded pure **8** (4.5 g, 62%); b.p. 125 °C (0.08 mm Hg); δ_H 1.3 (t, 3 H, J = 7 Hz, CH_3CH_2), 1.65 (s, 3 H, CH_3C=), 3.2 (s, 2 H, CH_2), 4.25 (q, 2 H, J= 7 Hz, CH_2-CH_3), 4.85 (s, 2 H, CH_2Ph), 6.15 (s, 1 H, CH=), 7.4 (s, 5 H, aromatic); ν_{max}/cm^{-1} 1720; MS: 235 $[M+1]^+$, 219 $[M-15]^+$, 205 $[M-29]^+$, 189 $[M-45]^+$, 128 $[M-106]^+$. $C_{14}H_{18}O_3$: Anal. found: C, 71.82; H, 7.65. Calc.: C, 71.79; H, 7.69 %.

(b) The unsaturated ester **8** (2.6 g, 11 mmol) was hydrogenated in ethyl acetate (30 mL) in the presence of 10% Pd/C (0.26 g). The extent of the reaction was monitored by ^{1}H-NMR and at the end, the mixture was filtered and the filtrate evaporated at reduced pressure to afford pure ester **9** (2.46 g, 95%); b.p. 130 °C (0.08 mm Hg); δ_H 0.95 (d, 3 H, J = 6 Hz, CH_3CH), 1.2 (t, 3 H, J=7 Hz, CH_3CH_2), 1.8 - 2.8 (m, 3 H, CH_2COO and CH-CH_2), 3.4 (d, 2 H, J = 5 Hz, CH-CH_2O), 4.15 (q, 2 H, J = 7 Hz , CH_2-CH_3), 4.5 (s, 2 H, CH_2Ph), 7.35 (s, 5 H, aromatic); ν_{max}/cm^{-1} 1715; MS: 208 $[M-28]^+$, 145 $[M-91]^+$, 129 $[M-107]^+$. $C_{14}H_{20}O_3$: Anal. found: C, 71.21; H, 8.51. Calc.: C, 71.18; H, 8.47%.

(c) The ester **9** (0.5 g, 2.11 mmol) in dry THF (5 mL) was added to a suspension of $LiAlH_4$ (0.16 g, 4.21 mmol) in dry THF (10 mL). The reaction was refluxed for 30 min and then to the reaction cooled at 0 °C water (0.16 mL), 15% NaOH (0.16 mL), and water (0.48 mL) were sequentially added. The reaction mixture was filtered on Celite, washed with diethyl ether and the organic solution dried and evaporated to give a residue (0.39 g) which was purified by distillation (150 °C at 0.2 mm Hg) to afford pure racemic **3a** (0.3 g, 73%). δ_H 0.95 (d, 3 H, J = 7 Hz, CH_3), 1.45 -2.25 (m, 3 H, CH_2CH), 2.9 (br s, 1 H, exchangeable), 3.45 (d, 2 H, J = 6 Hz, CH_2-OCH_2Ph), 3.75 (t, 2 H, J = 7 Hz, CH_2OH), 4.6 (s, 2 H, PhCH_2), 7.45 (s, 5 H, aromatic); ν_{max}/cm^{-1} 3400. MS: 194 $[M]^+$, 175 $[M-18]^+$, 105 $[M-89]^+$. $C_{12}H_{18}O_2$: Anal. found: C, 74.25; H, 9.31. Calc.: C, 74.22; H, 9.28%.

Enzymatic Transacetylation of (R,S)-1,4-Diol 1a and Derivatives 2a and 3a

General procedure. To a solution of (R,S)-alcohol (2 mmol) in chloroform (4 ml), vinylacetate (0.74 mL, 8 mmol) and PFL (22 mg, 42 U/mg) were added. The suspension was kept at 30 °C for the time necessary to reach 40% and 60% conversion to acetate respectively. The enzyme was removed by filtration and the mixture consisting of the unreacted alcohol and the corresponding acetate was purified by column chromatography using as eluants hexane/ethyl acetate mixtures with the ratio indicated below. The optically active alcohol was characterized and, in the case of compounds **2a** and **3a**, trasformed into the corresponding MTPA ester, following the same protocol applied to the corresponding racemate. Thus, a solution of the alcohol (0.1 mmol) was reacted with (S)-(+)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (MTPA-Cl) as described in Ref. 8.

Transacetylation of Diol 1a

(a) The enzymatic reaction of the racemic diol **1a** (0.208 g) was stopped after 4 h when 34% of the unreacted diol **1a** was present in the mixture (monitored by GLC). The diacetate **1d** (15%) and the mixture of monoacetates **1b** and **1c** (50%) were also present. The retention times for a oven temperature of 130 °C were 4.54, 6.61, 6.67, 10.48 min for **1a**, **1b**, **1c**, and **1d**, respectively. The mixture was purified by column chromatography and the racemic diacetate **1d** was eluted with hexane/ethyl acetate (8:2) (0.042 g, 11%); δ_H 1.0 (d, 3 H, CH_3CH), 1.5 - 2.4 (m+s, 9 H, CH_2CH and CH_3CO), 3.95 - 4.45 (d+t, 4 H, CH_2OCOCH_3); ν_{max}/cm^{-1} 1740. The mixture of monoacetates **1b** and **1c** (0.068 g, 24%) was eluted with hexane/ethyl acetate (1:1). ^{1}H NMR (500 MHz): δ_H 0.91 - 0.96 (two overlapped doublets, 3 H, CH_3-CH), 1.45 - 1.65 (m, 2 H, CH_2-CH_2O), 1.75 - 1.9 (m, 1 H, *CH*), 2.01 (s, 0.9 H, CH_3-COO-CH_2-CH_2 corresponding to 30% of the 4-acetate **1c**), 2.02 (s, 2.1 H, CH_3-COO-CH_2-CH corresponding to 70% of the 1-acetate **1b**), 3.44 - 3.48 (m, 0.6 H, CH_2OH of compound **1c**), 3.62 - 3.73 (m, 1.4 H, CH_2-OH of compound **1b**), 3.85 - 3.95 (m, 1.4 H, CH_3COO-CH_2 of compound **1b**), 4.05 - 4.15 (m, 0.6 H, CH_3-COO-CH_2 of compound **1c**), 4.65 (s, 1H, exchangeable). Elution with dichloromethane/methanol (9:1) afforded the pure diol (R)-(+)-**1a** (0.05 g, 24%). δ_H 0.9 (d, 3 H, CH_3CH), 1.3 - 2.1 (m, 3 H, CH_2CH), 3.3-4.0 (m, 4 H, CH_2O), 4.0 - 4.4 (m, 2 H, exchangeable); ν_{max}/cm^{-1} 3300; $[\alpha]_D$ +9 (*c* 1, CH_3OH) [lit. +13.2 for optically pure **1a** in the same conditions].[11]

(b) The enzymatic reaction was stopped after 24 h when the unreacted diol **1a** disappeared. The products were the racemic diacetate **1d** (60%) and the mixture of monoacetates **1b** and **1c** (40%). By purification on column chromatography, the mixture of monoacetates **1b** and **1c** (0.063 g, 22%) was eluted with hexane/ethyl acetate (1:1). By 500 MHz ^{1}H NMR a ratio 7:3 was established again for the two monoacetates **1b** and **1c**, respectively. A solution of the above mixture in dry THF (5 mL) was added to a suspension of $LiAlH_4$ (0.065 g, 1.71 mmol) in dry THF (5 mL). The reaction was refluxed for 30 min and then to the reaction cooled at 0 °C water (0.065 mL), 15% NaOH (0.065 mL) and water (0.195 mL) were sequentially added. The work-up as previously described afforded pure (R)-(+)-**1a** (0.03 g, 67%); $[\alpha]_D$ +2.5 (*c* 1, CH_3OH).

(R)-(+)-4-Benzyl Ether 2a

Reaction time 3 h; elution with hexane/ethyl acetate (1:1); yield 38%. The chemico-physical data were in agreement with those reported for the racemic material. $[\alpha]_D$ +9.8 (*c* 4, C_2H_5OH) [lit. value +10.1, as reported in Ref. 14]. For the evaluation of the enantiomeric excess by ^{1}H-NMR (500 MHz), in the spectrum of the MTPA ester of racemic **2a** we considered the signals corresponding to the CH_2-O-MTPA moiety (ten signals between 4.085 and 4.275 ppm). For the enzymatically prepared (R)-(+)-**2a**, the above signals were simplified and only a doublet at 4.175 ppm was present.

(S)-(+)-Acetate 2b

Reaction time 5 h; elution with hexane/ethyl acetate (9:1); yield 38%. $[\alpha]_D$ +2.4 (*c* 1, CH_3OH); δ_H 1.0 (d, 3 H, J = 7 Hz, CH_3CH), 1.1 - 2.0 (m, 3 H, CH_2CH), 2.05 (s, 3 H, CH_3CO), 3.6 (t, 2 H, J = 6 Hz, CH_2OCH_2Ph), 4.0 (d, 2 H, CH_2OAc), 4.55 (s, 2 H, CH_2Ph), 7.35 (s, 5H, aromatic).

In order to establish the configuration, the acetate **2b** (0.332 g, 1.41 mmol) was dissolved in dry THF (5 mL) and the solution was added to a suspension of $LiAlH_4$ (0.16 g, 4.23 mmol) in dry THF (10 mL). The reaction was refluxed for 30 min and then to the reaction cooled at 0 °C and worked up as described for the hydrolysis of the monoacetes **1b** and **1c** to the diol **1a**. The final residue was purified by chromatography,

and elution with hexane/ethyl acetate (8:2) gave (S)-(-)-**2a** (0.23 g, 85%); $[\alpha]_D$ -8.6 (*c* 4, C_2H_5OH). The enantiomeric excess was determined by 500 MHz ^{1}H-NMR analysis of its MTPA ester, as for the above (R)-(+)-**2a**. In the present case, the signals at 4.183 (d) and the complex of the couple of four signals centered at 4.110 and 4.258 were in a 7.5:92.5 ratio, thus establishing an optical purity of 85% for the starting acetate **2b**.

(R)-(-)-1-Benzyl Ether 3a

Reaction time 4 h; elution with hexane/ethyl acetate (1:1); yield 38%; $[\alpha]_D$ -0.9 (*c* 1, CH_3OH). The chemico-physical data were in agreement with those reported for the racemic material. In order to establish the configuration of (-)-**3a**, a sample prepared by the enzymatic reaction (0.091 g, 0.47 mmol) was hydrogenated in ethyl acetate (10 mL) in the presence of 10% Pd/C (50 mg). The reaction was monitored by ^{1}H-NMR and, at the end, the mixture was filtered and the filtrate evaporated at reduced pressure to afford pure (R)-(+)-**1a** (0.043 g, 88%); $[\alpha]_D$ +3.8 (*c* 1, CH_3OH). The extent of the ee was established by comparison of the 500 MHz ^{1}H-NMR spectrum of the MTPA esters of racemic and (R)-(-)-**3a** employing the decoupling technique. By decoupling the CH signal at 1.87 ppm, the resonances for the methyl group are simplified into two broad singlets at 0.925 and 0.936 ppm. By the same procedure, in the spectrum of the MTPA ester from enzymatically prepared **3a** the two singlets were in the ratio of 3:7, respectively. This established an optical purity of 40% for the compound (R)-(-)-**3a**.

(S)-(-)-Acetate 3b

Reaction time 6 h; elution with hexane/ethyl acetate (8:2); yield 38%; $[\alpha]_D$ -1.3 (c 1, CH_3OH). δ_H 1.05 (d, 3 H, J = 7 Hz, CH_3CH), 1.35-2.25 (m, 3 H, CH_2-CH), 2.1 (s, 3 H, CH_3CO), 3.4 (d, 2 H, J = 6 Hz, CH_2OCH_2Ph), 4.25 (t, 2 H, J = 7 Hz, CH_2OAc), 4.6 (s, 2 H, CH_2Ph), 7.45 (s, 5 H, aromatic). In order to establish the configuration, a solution of enzymatically prepared (R)-(-)-**3a** ($[\alpha]_D$ -0.9, 0.2 g, 1.03 mmol) in pyridine (1 mL) was treated with acetic anhydride (0.3 mL) at room temperature (18 h). After an usual work-up, the residue (0.23 g) was purified by chromatography to afford (R)-(+)-**3b** (0.194 g, 80%); $[\alpha]_D$ +1 (*c* 1, CH_3OH).

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previous name for the sake of homogeneity with our previous results.

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