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ENANTIOSELECTIVE TRANSESTERIFICATION OF 2-METHYL-1,3-PROPANEDIOL DERIVATIVES CATALYZED BY *Pseudomonas fluorescens* LIPASE IN AN ORGANIC SOLVENT

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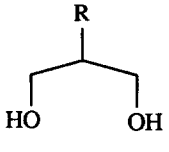
Abstract. - The irreversible transesterification of racemic 2-methyl-1,3-propanediol derivatives, the monoethers **3a**, **3b**, **5a**, and the monobenzoate **5b**, with vinyl acetate catalyzed by *Pseudomonas fluorescens* lipase in chloroform affords enantiomerically pure chiral synthons.

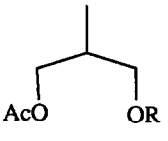
Introduction

Chiral monoesters of prochiral 2-substituted-1,3-propanediols **1** are valuable synthons for the preparation of natural products like muscone,[1] microbial growth factors, *i.e.* the (-)-A-factor,[2,3] or a renin inhibitor.[4,5] A biocatalytic approach to the enantioselective synthesis of the above chiral building blocks can be constituted by the enzymatic transesterification of the prochiral 1,3-diols **1**, which could be realized in an organic solvent using vinyl acetate as irreversible acyl donor in the presence of various lipases.[6,7]



1

a. R=CH_3
b. R=CH_2-CH=CH_2
c. R=CH_2Ph



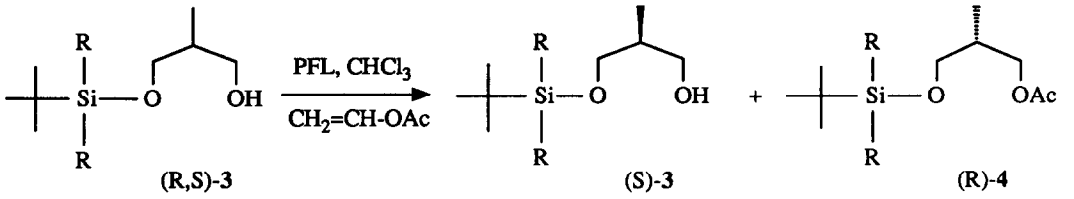
2

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

However, from the published data it appears that the above reaction can be enantioselective when applied to various 1,3-propanediols substituted with relatively bulky groups like **1b**[3,4] or **1c**.[4,5] Less clearcut results have been obtained when the substituent at the position 2 is a methyl group, as in 2-methyl-1,3-propanediol **1a**.[4,8] In fact, carrying out the transesterification procedure in vinyl acetate as solvent and *Pseudomonas fluorescens* lipase (PFL) as biocatalyst, a 60% enantioselectivity was reported.[4] We have found that, unless a special care was used for the experimental conditions, the monoacetate **2a** could not be obtained in higher enantiomeric excess (ee), also carrying out the reaction in chloroform. The optically pure (S)-monoacetate **2a** (>98% ee) could be prepared only if the diol **1a** completely reacted and 60% of diacetate **2b** and 40% of monoacetate **2a** were formed.[8] We also found that the racemic monoacetate **2a** itself was a good substrate for the same enzymatic resolution and from this reaction, the (S)-monoacetate **2a** (>98% ee) was recovered as unreacted material together with the achiral diacetate **2b** as the product of acetylation.[8]

PFL-Catalyzed Resolution of 2-Methyl-1,3-propanediol Monosilyl Ethers 3a and 3b.

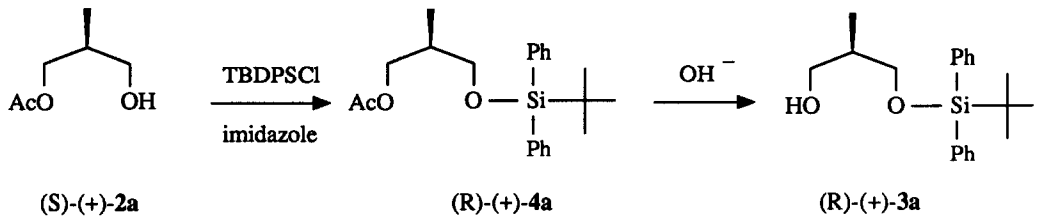
In the previous paper,[8] the main goal was the desymmetrization of the prochiral diol **1a** and the preparation of the chiral monoacetate **2a**, which was used as the intermediate for the synthesis of other chiral synthons, mainly the silyl ethers **3a** and **3b**, as well as the corresponding enantiomeric acetates **4**. We also observed that the racemic *t*-butyl diphenylsilyl ether (TBDPS) **3a** was a good substrate for the enzymatic transesterification and our preliminary results showed that the (R,S)-TBDPS **3a** could be resolved into nearly enantiomerically pure (-)-alcohol **3a** and (+)-acetate **4a** (Scheme 1).[10]



a. R=Ph ; **b.** R=CH_3

Scheme 1

The configurations of (-)-**3a** and (+)-**4a** were established by comparison of their optical rotations with those recorded for compounds of known configuration obtained from the enzymatically prepared (S)-(+)-acetate **2a**.[8] In fact, silylation[11] of enzymatically prepared (S)-(+)-**2a** afforded the (R)-(+)-acetate **4a** and the alkaline hydrolysis of this acetate, afforded (R)-(+)-**3a**, which is, therefore, the enantiomer of the enzymatically prepared (-)-**3a** (Scheme 2).

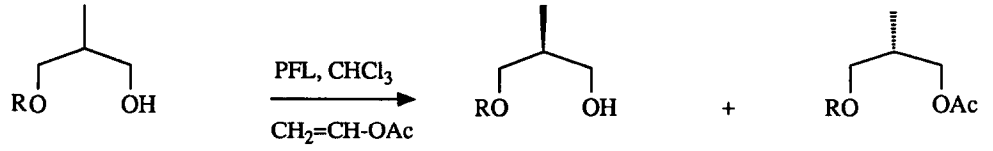


Scheme 2

Thus, the compound (-)-**3a** is in (S)-configuration and the extent of its ee, as well as that of the acetate **4a** was 98%, as calculated from the value of their optical rotations. In order to extend our studies on the PFL-catalyzed transesterification to other 2-methyl-1,3-propanediol derivatives of synthetic significance as chiral building blocks, we prepared other racemic monoderivatives of the diol **1a**. Interestingly, the racemic silyl ethers **3a** and **3b**, as well as the benzyl ether **5a** and the esters **2a** and **5b**, could be prepared in good yields by reaction of the diol **1a** with the stoichiometric amount of reactant. Thus, following published procedures, the *t*-butyldiphenylsilyl (TBDPS)[11] and *t*-butyldimethylsilyl (TBDMS)[12] ethers **3a** and **3b** were prepared from **1a** in 79 and 84% yields, respectively. An intramolecular hydrogen bond may be present in the

diol **1a** dissolved in some organic solvents, as it can be suggested by the ^{1}H-NMR spectra of the diol in CD_3OD and in $CDCl_3$. This fact probably makes one hydroxyl group more available in all the mediums in which the reactions are carried out. For the experimental conditions of the enzymatic reaction, we had already experienced on similar compounds[13] that the maximum ee of the alcohol could be obtained carrying out the acetylation to a 60% extent. In this way, the unreacted alcohol (40%) could be obtained nearly optically pure, whereas the maximum ee for the enantiomeric acetates was reached when the transacetylation was stopped at 40% conversion. Also the enzymatic resolution of racemic TBDMS derivative **3b** afforded the nearly optically pure unreacted alcohol, (S)-(-)-**3b**, and the (R)-(+)-acetate **4b** (both 98% ee). The configuration of **3b** was assigned from the optical rotation[14] and the ee established by the 500 MHz ^{1}H-NMR analysis of its MTPA ester,[15] as previously described.[8] Acetylation of (S)-(-)-**3b** furnished the corresponding acetate for the determination of the configuration and optical purity of (R)-(+)-**4b**.

PFL-Catalyzed Resolution of 2-Methyl-1,3-propanediol Monobenzyl Ether 5a and Monobenzoate 5b. Sodium hydride was required for the reaction of the diol **1a** with benzyl or benzoyl chloride, to afford the racemic benzyl ether **5a** and benzoate **5b** in 87 and 84% yields, respectively. The enzymatic resolution of the racemic benzyl ether **5a** afforded the unreacted alcohol (S)-(+)-**5a** and the (S)-(+)-acetate **6a**,[16] both 90% ee. The benzyl ether **5a** is an important chiral building block which has been prepared by different approaches.[17] The configuration of **5a** was assigned on the basis of its optical rotation and the ee checked by ^{1}H-NMR analysis of its MTPA ester. The hydrolysis of the (S)-(+)-acetate **6a** afforded the (R)-(-)-alcohol **5a** and the ee of this compound was determined again by ^{1}H-NMR analysis of its MTPA ester. Finally, also the racemic monobenzoate **5b** could be resolved into the (+)-alcohol **5b** and the corresponding (-)-acetate **6b** (Scheme 3).



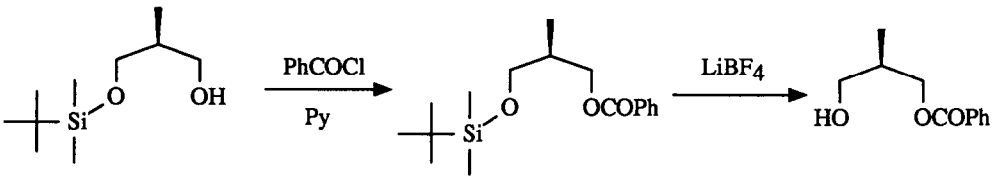
(R,S)-**5** (S)-**5** **6**

a. R=$PhCH_2$; **b.** R=PhCO

Scheme 3

The ee of the benzoate alcohol **5b** was established by the ^{1}H-NMR of its MTPA ester (84%) but, to our knowledge, the optically pure benzoate **5b** has not been previously reported. Therefore, we prepared a reference sample of known configuration. The optically pure (S)-acetate **2a** could, in principle, be used for this correlation, *via* benzoylation to **6b** and hydrolysis to the optically active benzoate **5b**. However, it is known that acyl migration may occur in the basic hydrolysis of similar 1,3-diol esters.[18] For this reason, we preferred to use as starting material the enantiomerically pure (S)-(-)-TBDMS **3b**, following the route depicted in Scheme 4.

The silyl ether (S)-**3b**, enzymatically prepared in 98% ee, was benzoylated to the compound **7** (86% yield)



(S)-**3b** **7** (R)-**5b**

Scheme 4

and the silyl group of the latest compound was selectively cleaved with lithium tetrafluoroborate.[19] The (R)-(-)-benzoate **5b** was obtained and we could conclude that the (+)-benzoate **5b** enzymatically prepared had the S configuration. Acetylation of the (S)-(+)-alcohol **5b** (84% ee) afforded the corresponding (S)-(+)-acetate **6b**, $[\alpha]_D$ +0.75°. From this low optical rotation, a possible value of 90% ee is suggested for the enzymatically prepared (R)-(+)-acetate **6b**.

All the results obtained using as substrates the derivatives of the diol **1a** are collected in the Table.

Table. PFL-Catalyzed Transesterification of 2-Methyl-1,3-propanediol Derivatives

Substrate	Alcohol[a] (h)	$[\alpha]_D$[b] (°)	ee[c] (%)	Acetate[d] (h)	$[\alpha]_D$[e] (°)	ee[f] (%)
2a	(S)-**2a** (3)	+9.8	98	**2b**	-	-
3a	(S)-**3a** (140)	-5.0	98	(R)-**4a** (100)	+1.3	98
3b	(S)-**3b** (24)	-11.0	98	(R)-**4b** (15)	+5.0	98
5a	(S)-**5a** (12)	+2.6	90	(S)-**6a** (8)	+4.9	90
5b	(S)-**5b** (5)	+2.1	84	(R)-**6b** (2)	-0.8	90

a) Unreacted alcohol recovered (38±2% yields) at 60% conversion to the corresponding acetate. The time necessary to reach this conversion is given in brackets. b) For concentration and solvent, see Experimental. c) Except **3a**, all the ee were established by NMR (see Ref. 15). d) Products recovered at 40% conversion (38±2% yields). The time necessary to reach this conversion is given in brackets. e) Optical rotations were recorded in the same conditions as for the alcohols. f) Optical purities determined by acetylation of optically active alcohols or hydrolysis of the acetates to the corresponding alcohols and comparison of optical rotations or analysis of MTPA esters (see Experimental).

Conclusions. We have found that all the monoesters and monoethers of 2-methyl-1,3-propanediol **1a** examined by us are efficiently resolved in an organic solvent by the PFL-catalyzed transesterification procedure. The enantioselectivity is excellent and by this approach a few synthetically valuable chiral compounds become available in both enantiomeric forms. The stereochemical outcome is the same for all the substrates and in agreement with the results obtained for other α-methyl alcohols.[13] The bulk of the above informations may furnish interesting indications on the possible topology of the active site of the lipase in organic solvents and needs to be integrated by more results from other structurally related compounds.

Experimental Section.

Pseudomonas fluorescens lipase (PFL), solvents and reagents were purchased from Fluka (Switzerland). Sodium hydride was available from Aldrich (U.S.A.) as powder (dry, 97% purity). 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. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. Distillations for analytical purposes were carried out on a glass tube oven Büchi GKR-50. Analytical TLC were performed on silica gel Merck 60 F254 plates and column chromatographies were performed on silica gel Merck 60 (230-400 mesh). MS analyses were performed using a Hewlett Packard Instrument Mod.5988 by direct inlet probe and electronic impact (electron energy at 70 eV and ion source at 270 °C) techniques. 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-1,3-propanediol 1a.- To a suspension of $LiAlH_4$ (10.2 g, 0.27 mol) in dry THF (250 mL), a solution of diethyl methylmalonate (12 g, 68.9 mmol) in dry THF was added and the mixture was refluxed (2 h). After cooling, water (10.2 mL), 15% NaOH (10.2 mL) and water (30.6 mL) were sequentially added and the suspension filtered onto Celite and washed with ether (200 mL). The solvent was dried and evaporated to afford an oil (5.9 g), which was purified by distillation (110 °C at 0.5 mm Hg) to give pure **1a** (4.8 g, 77%); ν_{max}/cm^{-1} 3300; δ_H (in CD_3OD) 0.76 (d, 3 H, J = 7 Hz, CH_3), 1.34-2.0 (m, 1 H, CH), 3.38 (d, 4 H, J = 6 Hz, CH_2), 4.84 (s, 2 H, exch.); δ_H (in $CDCl_3$) 0.90 (d, 3 H, J = 7 Hz, CH_3), 1.60-2.35 (m, 1 H, CH), 3.70 (t, 2 H, J = 5 Hz, CH_2 superimposed to exchangeable hydrogen), 4.10 (t, 2 H, J = 5 Hz, CH_2). $C_4H_{10}O_2$: Anal. found: C, 53.45; H, 11.15; Calc.: C, 53.33; H, 11.11%.

Synthesis of Racemic Monoesters 2a, 5b and Monoethers 3a, 3b, 5a.

Monoacetate 2a.- 2-methyl-1,3-propanediol **1a** (1 g, 11.1 mmol) was dissolved in pyridine (5 mL) and acetic anhydride (1 g, 9.8 mmol) was added under vigorous stirring. The reaction was left 4h at room temperature, then water (20 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3x30 mL). The organic phase was dried and evaporated to give 1.37 g of a crude product, that was purified by silica gel column (hexane/ethyl acetate, 6/4) to afford pure **2a** (1.15 g, 78%). B.p. 90°C (0.5 mm Hg); ν_{max}/cm^{-1} 3160, 3300-3100, 1730; δ_H 0.98 (d, 3 H, J = 7 Hz, CH_3), 2.08 (s + m, 4 H, CH_3CO and CH), 3.6 (d, 2 H , J = 6 Hz, CH_2OH), 4.16 (d, 2 H, J = 6 Hz, CH_2OCO), 4.78 (s, 1 H, exch.); $C_6H_{12}O_3$: Anal. found: C, 54.64; H, 9.22; Calc.: C, 54.52; H, 9.16.

Monobenzoate 5b.- A solution of the diol **1a** (0.8 g, 8.9 mmol) in dry THF (2 mL) was added with stirring at room temperature to a suspension of NaH (0.256 g, 10.68 mmol) in dry THF (20 mL). The reaction was left under stirring at room temperature for 0.5 h then benzoyl chloride was added (1.5 g, 10.68 mmol). After 2h at room temperature, water was added, THF evaporated at reduced pressure and the aqueous phase extracted with CH_2Cl_2 (3x20 mL) to give 2.2 g of crude product. After column chromatography (hexane/ethyl acetate, 6/4), pure **5b** was obtained (1.46 g, 84%); b.p. 210-215°C (0.1 mm Hg); ν_{max}/cm^{-1} 3630, 3490, 1715; δ_H 1.1 (d, 3 H, J = 7 Hz, CH_3), 1.9- 2.6 (m, 1 H, CH), 3.1 (s, 1H, exch.), 3.7 (d, 2 H, J = 6 Hz, CH_2OH), 4.45 (d, 2 H, J = 6 Hz, CH_2OCO), 7.4 - 8.5 (m, 5 H, aromatic); MS: 193 $[M-1]^+$, 176 $[M-18]^+$, 164 $[M-30]^+$, 149 $[M-45]^+$, 123 $[M-71]^+$, 105 $[PhCO]^+$. $C_{11}H_{14}O_3$: Anal. found: C, 68.12; H, 7.35; Calc.: C, 68.02; H, 7.26.

Monosilyl Ethers 3a and 3b.- To a solution of the diol **1a** (0.5 g, 5.5 mmol) in dry THF (5 mL) t-butyldiphenylchlorosilane (1.5 g, 5.5 mmol) or t-butyldimethylchlorosilane (0.829 g, 5.5 mmol) and

imidazole (0.756 g, 11.1 mmol) were added. The reaction was kept under stirring at 40 °C for 4 h, then water was added (5 mL) and THF evaporated. The aqueous phase was extracted with CH_2Cl_2 (3x 10 mL), the organic phase dried and evaporated to give 0.7 g of crude product, purified on a silica gel column (hexane/ethyl acetate, 8/2) to afford pure **3a** (1.425 g, 79% yield) or **3b** (0.942 g, 84% yield). ***TBDPS 3a***: δ_H 0.85 (d, 3 H, J = 7 Hz, CH_3), 1.2 (s, 9 H, $(CH_3)_3C$), 1.8 (m, 1 H, CH), 2.75 (s, 1 H, exch.), 3.6 - 3.9 (m, 4 H, CH_2OH and CH_2OSi), 7.3 - 7.95 (m, 10 H, aromatic); MS: 271 $[M-57]^+$, 257 $[M-71]^+$, 239 $[M-90]^+$. $C_{20}H_{28}O_2Si$: Anal. found: C, 73.21; H, 8.65; Calc.: C, 73.12; H, 8.59. ***TBDMS 3b***: δ_H 0.0 (s, 6 H, $(CH_3)_2Si$), 0.65 - 1.2 (s + d, 12 H, $(CH_3$-CH and $(CH_3)_3CSi$), 1.65 - 2.15 (m, 1 H, CH), 2.85 (broad, 1 H, exch.), 3.4 - 3.8 (m, 4 H, CH_2OH and CH_2OSi); $C_{10}H_{24}O_2Si$: Anal. found: C, 58.88; H, 11.92; Calc.: C, 58.77; H, 11.83.

Monobenzyl Ether 5a.- A solution of the diol **1a** (0.56 g, 6.22 mmol) in dry THF (2 mL) was added under vigorous stirring at room temperature under nitrogen, to a suspension of NaH (0.183 g, 7.63 mmol) in dry THF (10 mL). The reaction was kept under stirring at room temperature for 0.5 h, then benzyl bromide (1.3 g, 7.63 mmol) in dry THF (5 mL) was added dropwise. The reaction was stirred at room temperature for 6h, then water was added and THF evaporated. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the organic phase dried and evaporated to afford 1.2 g of crude product, purified by silica gel column (hexane/ethyl acetate, 7/3). Pure **5a** (0.98 g, 87%) was obtained, b.p. 210 °C (0.2 mm Hg); ν_{max}/cm^{-1} 3500; δ_H 0.9 (d, 3 H, J = 7 Hz, CH_3CH), 1.8 - 2.3 (m, 1 H, CH), 3.2 (1 H, exch.), 3.4 - 3.75 (dd, 4 H, CH_2OH and $\underline{CH_2}OCH_2Ph$), 4.5 (s, 2 H, CH_2Ph), 7.3 (s, 5 H, aromatic); $C_{11}H_{16}O_2$: Anal. found: C, 73.38; H, 9.02; Calc.: C, 73.30; H, 8.95.

Enzymatic Transacetylation of (R,S)-1,3-Diol Derivatives: General Procedure.- To a solution of the (R,S)-alcohol (1 mmol) in chloroform (2 mL), vinylacetate (0.37 mL, 4 mmoles) and PFL (11 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 (Table). The enzyme was removed by filtration and, after evaporation, the mixture of the unreacted alcohol and the corresponding acetate was purified by silica gel (40:1, weight) column chromatography (hexane/ethyl acetate, 9/1 and 8/2). Generally the optically active alcohols and acetates were recovered in 38±2% yields. For the determination of the ee by 500 MHz ^{1}H-NMR, the MTPA esters were prepared according the following experimental protocol. A solution of the alcohol (0.1 mmol) in carbon tetrachloride (0.6 mL) was treated with pyridine (0.6 mL) and (S)-(+)-MTPA-Cl (J.P.S., Switzerland, 0.025 g, 0.1 mmol). After 18 h at room temperature, 3-dimethylamino-1-propylamine (0.04 mL) and dichloromethane (1 mL) were added. The organic phase was washed with 1 N HCl, saturated sodium carbonate, dried and evaporated.

(S)-(+)-Acetate 2a.- The chemico-physical data were in agreement with those of the racemic compound **2a**; $[\alpha]_D$ +9.8° (*c* 2, EtOH)[8]. In the NMR of the MTPA ester from the racemic **2a**: δ_H two doublets centered at 0.94 and 0.96 ppm (CH_3CH); in the spectrum of the MTPA ester of (S)-(+)-**2a** only the doublet centered at 0.94 ppm could be detected.

(S)-(-)-TBDPS Alcohol 3a.- The chemico-physical data were in agreement with those of (R,S)-**3a**; $[\alpha]_D$ -5° (*c* 2, $CHCl_3$).

(R)-(+)-TBDPS Acetate 4a.- B.p. 215 °C (13 mm Hg); ν_{max}/cm^{-1} 1730; $[\alpha]_D$ +1.3° (*c* 2, $CHCl_3$); δ_H 0.95 (d, 3 H, J = 7 Hz, CH_3CH), 1.1 (s, 9 H, $(CH_3)_3C$), 1.8 - 2.4 (m, 1 H, CH), 2.0 (s, 3 H, CH_3CO), 3.65

(d, 2 H, J = 6 Hz, CH_2OSi), 4.15 (d, 2 H, J = 6 Hz, CH_2OAc), 7.25 - 8.0 (m, 10 H, aromatic); MS: 371 $[M+1]^+$, 313 $[M-57]^+$, 293 $[M-77]^+$, 271 $[M-100]^+$. $C_{22}H_{30}O_3Si$: Anal. found: C, 71.42; H, 8.26; Calc.: C, 71.31; H, 8.16. The values of the optical rotations of enantiomerically pure **3a** and **4a** were calculated from the $[\alpha]_D$ of (R)-(+)-**4a** and (R)-(+)-**3a** prepared from the (S)-(+)-acetate **2a** (see the following procedure for the determination of the configuration of enzymatically prepared (S)-TBDPS **3a**).

(S)-(-)-TBDMS Alcohol 3b.- The chemico-physical data were in agreement with those of (R,S)-**3b**; $[\alpha]_D$ -11° (*c* 0.6, $CHCl_3$). The optical rotation of (R)-(+)-**3b** was +11° in the same conditions.[8]

(R)-(+)-TBDMS Acetate 4b.- B.p. 100 °C (0.3 mm Hg); ν_{max}/cm^{-1} 1730 cm^{-1}; δ_H 0.0 (s, 6 H, $(CH_3)_2Si$), 0.9 - 1.0 (d +s, 12 H, $(CH_3)_3C$ and CH_3CH), 1.8 - 2.15 (m, 1 H, CH), 2.1 (s, 3 H, CH_3CO), 3.6 (d, 2 H, J = 6 Hz, CH_2OSi), 4.1 (d, 2 H, J = 7 Hz, CH_2OAc); $C_{12}H_{26}O_3Si$: Anal. found: C, 58.58; H,10.72; Calc.: C, 58.49; H, 10.64. A sample of pure (R)-(+)-**4b** showed $[\alpha]_D$ +5° (*c* 0.6, $CHCl_3$) and was compared with the acetate obtained from enzymatically prepared (S)-(-)-**3b**. The optical rotation for (S)-(-)-**4b** was -5° (*c* 0.6, $CHCl_3$).

(S)-(+)-Benzyloxy Alcohol 5a.- The chemico-physical data were in agreement with those reported in the literature[17]; $[\alpha]_D$ +2.6° (*c* 2.2, EtOH). In the NMR of the MTPA ester from the racemic **5a**: δ_H two doublets centered at 0.94 and 0.96 ppm for CH_3CH. In the spectrum of the MTPA ester of (S)-(+)-**5a** the two doublets at 0.94 and 0.96 ppm were in the ratio of 5:95.

(S)-(+)-Benzyloxy Acetate 6a.- B.p. 175-185 °C (13 mm Hg); $[\alpha]_D$ +4.9° (*c* 2.2, EtOH); ν_{max}/cm^{-1} 1725; δ_H 0.98 (d, 3 H, J = 7 Hz, CH_3CH), 1.8 - 2.4 (m, 1 H, CH), 2.05 (s, 3 H, CH_3CO), 3.65 (d, 2 H, J = 6 Hz, $\underline{CH_2}O\text{-}CH_2Ph$), 4.15 (d, 2 H, J= 6 Hz, CH_2OAc), 4.55 (s, 2 H, CH_2Ph), 7.4 (s, 5 H, aromatic); $C_{13}H_{18}O_3$: Anal. found: C, 70.33; H, 8.27; Calc.: C, 70.24; H, 8.16.

$LiAlH_4$ reduction of (S)-(+)-**6a** afforded a sample of (R)-alcohol **5a**, $[\alpha]_D$ -2.5° (*c* 1.5, EtOH). The NMR of the MTPA ester from (R)-(-)-**5a** MTPA ester showed two doublets centered at 0.94 and 0.96 (95:5 ratio).

(S)-(+)-Benzoate Alcohol 5b.- The chemico-physical data were in agreement with those reported for the racemic material; $[\alpha]_D$ +2.1° (*c* 1, MeOH). In the NMR of the MTPA ester from the racemic **5b**: δ_H two doublets centered at 0.95 and 1.05 ppm for the CH_3CH. In the spectrum of the MTPA ester of (S)-(+)-**5b** the doublets centered at 0.95 and 1.05 ppm were in a 8:92 ratio.

(R)-(-)-Benzoate Acetate 6b. B.p. 195-200 °C (13 mm Hg);$[\alpha]_D$ -0.8° (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 1720; δ_H 1.15 (d, 3 H, J = 7 Hz, CH_3CH), 2.1 (s, 3 H, CH_3CO), 2.0 - 2.7 (m, 1 H, CH), 4.25 (d, 2 H, J = 6 Hz, CH_2OAc), 4.4 (d, 2 H, CH_2OCOPh), 7.5 - 8.4 (m, 5 H, aromatic). Acetylation of the previous (S)-(+)-**5b** (84% ee) afforded a sample of pure (S)-(+)-**6b**, $[\alpha]_D$ +0.75° (*c* 0.6, $CHCl_3$); MS: 236 $[M]^+$, 193 $[M-43]^+$, 176 $[M-60]^+$, 134 $[M-102]^+$, 105 $[PhCO]^+$. $C_{13}H_{16}O_4$: Anal. found: C, 66.16; H, 6.92; Calc.: C, 66.08; H, 6.83.

Determination of the Configuration of Enzymatically Prepared (S)-(-)-TBDPS-3a.

To a solution of (S)-(+)-acetate **2a** (0.16 g, 1.2 mmol, $[\alpha]_D$ +9.1°, 91% ee) in dry THF (3 mL), *t*-butyldiphenylchlorosilane (0.399 g, 1.45 mmol) and imidazole (0.196 g, 2.88 mmol) were added. The reaction was kept under stirring at 40°C for 4 h, then water was added (1 mL) and THF evaporated. The product was extracted with dichloromethane (3 x 3 mL) and the acetate **4a** (0.43 g, 97%) was pure by NMR. The spectrum was identical to that obtained for the enzymatically prepared (R)-(+)-**4a**; $[\alpha]_D$ +1.2° (*c* 2, $CHCl_3$). The solution of (R)-(+)-**4a** in methanol (2.5 mL) was added to a 10% aqueous solution of

sodium carbonate (2.5 mL). After 4 h reflux, the solution was cooled, brought to neutrality and methanol evaporated. The product **3a** was extracted with dichloromethane (3x 1 mL), the organic phase dried and evaporated to give 0.383 g of crude product, purified on a silica gel column (hexane/ethyl acetate, 8/2) to afford pure (R)-(+)-**3a** (0.21 g, 53% from **2a**); $[\alpha]_D$ +4.5° (*c* 2, $CHCl_3$). From this value, the rotation for optically pure **3a** was established as +5.0° (*c* 2, $CHCl_3$).

Determination of the Configuration of Enzymatically Prepared (S)-(+)-Benzoate-5b.

(S)-(-)-TBDMS **3b** (0.051 g, 0.25 mmol; $[\alpha]_D$ -11.0° corresponding to 98% ee) was dissolved in pyridine (1.3 mL) and benzoyl chloride (0.045 g, 0.32 mmol) was added. After 6h at room temperature the reaction was poured in water and extracted with dichloromethane (1 x 3 mL). The organic phase was dried and evaporated to give pure **7** (0.066 g, 86%), which was not characterized and directly used in the next step. This compound was dissolved in CH_3CN/CH_2Cl_2 (1/2, v/v, 8 ml) and $LiBF_4$ (0.065 g, 0.69 mmol) was added. The reaction was stirred for 5 h at room temperature, then water was added, the organic phase evaporated and the aqueous phase was extracted with dichloromethane (3 x 3 mL). The solvent was dried and evaporated to afford a residue, purified on a column chromatography (hexane/ethyl acetate, 8 :2) to afford pure (R)-(-)-**5b** (0.04 g, 82% from **3b**); $[\alpha]_D$ -2.5° (*c* 1, MeOH). The chemico-physical data of the product were in agreement with those reported for the racemic material.

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