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# Baker's Yeast-Mediated Reduction of α-Hydroxy Ketones and Derivatives: The Steric Course of the Biotransformation

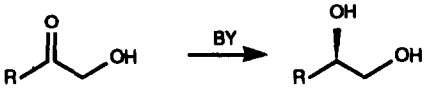
**Patrizia Ferraboschi, Paride Grisenti, Ada Manzocchi, Enzo Santaniello**

Dipartimento di Chimica e Biochimica Medica, Università degli Studi di Milano
Via Saldini, 50 - 20133 Milano, Italy

***Abstract.*** - The results from the baker's yeast-mediated reduction of the acetates **3a-d** and the methyl ethers **5a-d** were compared with the same biotransformation which converts the α-hydroxy ketones **1a-d** into the (R)-diols **2a-d** (90-98%ee); the acetates **3a-d** afford the (S)-monoacetates **4a-d** (72-94% ee) and the methyl ethers **5a-d** are reduced to the (R)-monoethers **6a-d** (64-76% ee).

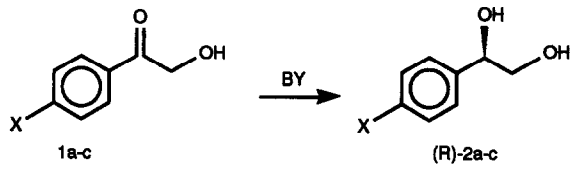
## *Introduction*

The reduction of carbonyl compounds by means of baker's yeast (*Saccharomyces cerevisiae*, BY) is one of the most popular biocatalytic methods used in organic synthesis for the preparation of enantiomerically pure hydroxy compounds.[1] The stereochemical outcome of the bioreduction follows the Prelog's rule[2] which assumes that if the carbonyl substituents are different in size [large (L) and small (S)] the reductase that accepts the substrate works with high enantioselectivity according to a defined stereochemistry.[3] However one cannot rely only on the Prelog's rule to predict the stereochemical outcome, since it is now well recognized that several oxidoreductases are present in BY,[4] and sometimes such enzymes reduce the same substrate with opposite stereochemistry.[5]




1 2

α-Hydroxy ketones **1** represent an exception to the above rule, since from the examples reported in the literature[6] all the substrates are enantioselectively reduced with high enantiomeric excess (ee) to the corresponding (R)-1,2-diols **2** by BY independently of the size of the carbonyl substituents. For instance, the aromatic hydroxy ketones **1a-c** are all reduced to the (R)-diols **2a-c** in high yields and 90-98% ee[6c,7] (Scheme 1).

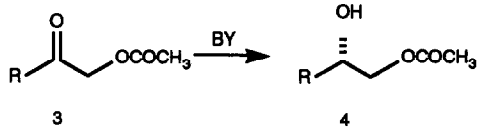



1a-c (R)-2a-c

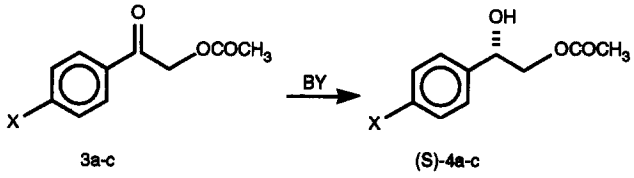
a. X = H b. X = $OCH_3$ c. X = Br

**Scheme 1**

For several BY biotransformations, it is sometimes possible to improve or invert the enantioselectivity by simple substrate manipulations.[8] This has also been observed for α-hydroxyketones[9] and, for instance, the acetates **3** are reduced to the 1,2-diol derivatives **4** and these (S)-monoacetates have the configuration opposite to that resulting for the 1,2-diols **2**[10] (Scheme 2).




3 4




3a-c (S)-4a-c

a. X = H b. X = $OCH_3$ c. X = Br

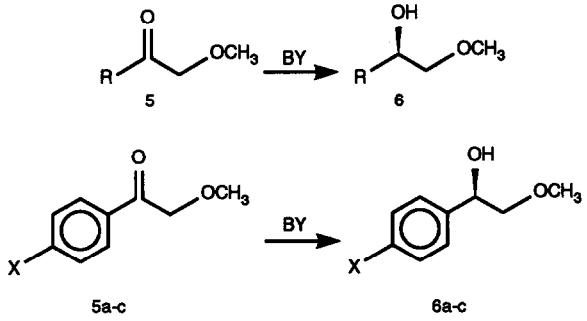
**Scheme 2**

The above protection as acetates suffers some drawback, since excellent results were obtained for compound **3a**,[10] but the enantioselectivity of the 4-methoxy analogue **3b** was lower compared to the reduction of the parent hydroxy ketone.[7a] The above protection cannot be expected to be of general synthetic application, since in the incubation conditions the acetate itself is susceptible to hydrolysis and other esters were even more easily hydrolyzed.[10] The above observations were confirmed by the BY-mediated bioreduction of the acetate **3c** to the corresponding (+)-monoacetate **4c** (34% yield). In order to establish the configuration and the ee it was necessary to prepare as a reference standard the optically pure (R)-(-)-diol **2c**, which is available by the BY reduction of the parent hydroxy ketone **1c** (44% yield).[11] The hydrolysis of the (+)-monoacetate **4c** afforded the (S)-(+)-diol **2c**, thus confirming that the BY-mediated reduction of the acetate **3c**, compared to that of the hydroxy ketone **1c**, occurs with an opposite

stereochemistry, but with lower ee (84%). This behaviour was also confirmed for aliphatic α-hydroxy ketones[12] and we decided to investigate the effect of a different protecting group.

***BY-Mediated Reduction of the of α-Hydroxy Ketones Methyl Ethers 5a-c***

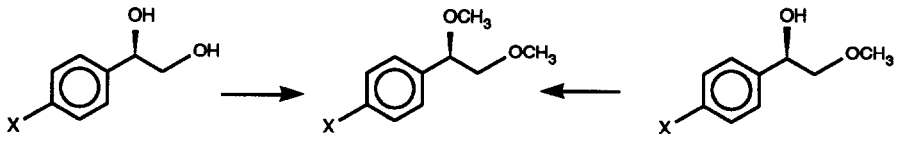
The choice of suitable derivative is severely limited by the fact that the enantioselectivity of the BY-mediated bioreduction of carbonyl compounds strongly depends on the size of substituents.[13] Therefore we planned to study the bioreduction of the methyl ethers **5**, since this group should convert the hydroxy into an apolar group of acceptable size for the enzymatic reducing system. The compound **5a** was prepared by the opening of stirene oxide with methanolic potassium hydroxide[14] and Jones' oxidation[15] of the resulting diol monomethyl ether. The methyl ethers **5b** and **5c** were obtained by displacement of the phenacyl bromides with sodium methoxide in methanol. The BY reduction of the methoxy ketones **5a-c** afforded the optically active 1-methyl ethers of the corresponding 1,2-diols, compounds **6a-c** (26-35% yield, Scheme 3).




a. X = H b. X = $OCH_3$ c. X = Br

**Scheme 3**

The ee of (-)-**6a-c** was 76, 74 and 64%, respectively, as estimated by 500 MHz $^1$H-NMR of the corresponding Mosher ester.[16] The optical rotations of the above methyl ethers **6a-c** were not found in the literature, and, for the determination of their absolute configuration, the preparation of standard monoethers from the corresponding optically active diols of known configuration should be set up. This synthesis, although possible, would require a lengthy procedure involving a chemoselective protection followed by deprotection. Alternatively, a partially selective methylation of the 1,2-diol should afford a mixture of 1- and 2-methyl ethers to be carefully separated. This was accomplished for the (R)-(-)-diol **2b** that was converted into the (-)-monoether **6b** (28%, after purification), showing that the BY reduction of **5b** affords the (R)-(-)-**6b**. For the configuration of **6a** and **6c**, we converted the (R)-1,2-diols **2a** and **2c**, prepared *via* the BY reduction of the hydroxyketones **1a** and **1c**, to the corresponding dimethyl ethers **7a** and **7c** (NaH, $CH_3I$ in THF, 52-68% yield). Comparison of the optical rotations of the above **7a** and **7c** with the same compounds prepared by methylation of monoethers **6a** and **6c** enabled us to assess for the latest compounds the (R)-configuration (Scheme 4). The (R)-configuration established for the three (-)-monoethers **6a-c** is the same as the diols obtained by reduction of the hydroxy ketones **1a-c** and opposite to that of the (S)-monoacetates **4a-c**. It was therefore clear that, depending on the protection of the hydroxy ketone, the bioreduction process can be directed towards different configurations of the products.




(R)-2
a. X = H c. X = Br

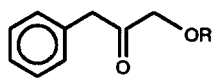
(R)-7

(R)-6

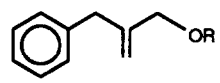
**Scheme 4**

***BY-Mediated Reduction of the α-Hydroxy Ketone 1d and its Derivatives 3d and 5d.***

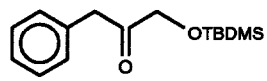
All the results and information available through the previous data do not provide a general picture for α-hydroxy ketones, due to the fact that in all the examined substrates the phenyl ring is directly attached to the carbonyl group and the results can be influenced by electronic effects.[17] Therefore, we chose the hydroxy ketone **1d** as model substrate and its acetate **3d** and the methyl ether **5d** as proper derivatives. We prepared compound **1d** in a most satisfactory way[18] starting from the allylic alcohol **8a**[19] protected as silyl ether **8b**. Ozonolysis of the latest compound afforded the protected hydroxy ketone **9** that gave the substrate **1d** after the removal of the silyl moiety (72% overall yield, Scheme 5). The acetate **3d** was easily prepared from the hydroxy ketone **1d** and the methyl ether **5d** was synthesized by methanolysis of the 3-phenyl-1,2-epoxypropane and Jones' oxidation of the resulting monomethyl ether.




1d R = H
3d R = $COCH_3$
5d R = $CH_3$




8
a. R = H b. R = TBDMS

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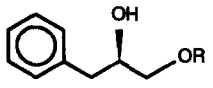
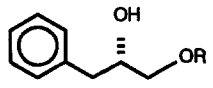
**Scheme 5**

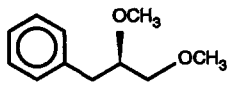
The results of the biotransformations (Scheme 6) show that the hydroxy ketone **1d** was efficiently (58% yield) transformed into the (R)-diol **2d** (95% ee). A short incubation time (3 hours) of the acetate **3d** allowed the isolation of the (S)-diol monoacetate **4d** (72% ee), whereas after longer times the main product was the (S)-diol **2d** with lower enantioselectivity (60% ee).[20] The bioreduction of the compound **5d** was less efficient (20% yield) and afforded the (R)-diol monoether **6d** with 72% ee. The R configuration for the compound **6d** was established preparing the (-)-dimethyl ether **10** from the (R)-(+)-diol **2d**, by comparison with the optical rotation of same compound obtained from the BY-prepared (+)-**6d**.




(R)-2d R = H 95% ee
(R)-6d R = $CH_3$ 72% ee




(S)-4d R = $COCH_3$ 72% ee
(S)-2d R = H 60% ee




(R)-10

**Scheme 6**

***Conclusions***

Our results clearly show that a simple protection of α-hydroxy ketones can direct the stereochemical outcome of the BY-mediated reduction towards a configuration which, depending on the protection, is the same or the opposite to that exhibited by the unprotected hydroxy ketones. The protection as acetate leads to the opposite configuration but suffers an undesirable hydrolysis side reaction, which lowers the yield of the biotransformation and leads to the diol as by-product which does not exhibit high ee. This is due to the fact that different and stereochemically conflicting processes are generating the product. The methyl ether protection could be the chemical solution to the above problem, but its size and nature does not fully satisfy the stereochemical demand of the enzyme(s), since the enantiomeric excess is never superior to 77%. Furthermore, the enzymatic reducing system which accepts the methyl ethers as substrates works with the same stereoselection to that required by the enzyme(s) which accepts the unprotected hydroxy ketone. Since it is well known that BY possesses a wide array of reductases,[5] it is very difficult to speculate which enzyme is responsible for the observed different bioreduction processes. In absence of this information, further complementary studies seem desirable to design the most satisfactory structure of the substrates, so that from a given carbonyl compound a specific bioreduction can be obtained as a consequence of simple chemical manipulation of the substrate.

***Experimental Section***

Solvents and reagents were purchased from Fluka (Switzerland). Unless otherwise indicated $^1$H-NMR refer to 60 MHz spectra, recorded on a Varian EM 360 L spectrometer for solution in $CDCl_3$, using $SiMe_3$ 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. Distillation 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 (70-230 mesh ASTM). The progress of some reactions were monitored by Hewlett-Packard GLC (Mod. 5988) on a capillary column (HP 5). The ee was determined by analysis of the MTPA esters, prepared according to the Mosher method by reaction of the alcohols with (S)-(+)-α-methoxy-α-trifluoromethyl phenylacetyl chloride. As a general procedure for the reaction work-up, 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.

***3-Phenyl-1-hydroxy-2-propanone 1d.*** - A solution of the allylic alcohol **8a**[19] (1.6 g, 10.8 mmol) in dry pyridine (2.6 mL) was treated with *t*-butyldimethylsilyl chloride (1.96 g, 13 mmol) at room temperature (4 h). Water (5 mL) was added and, after extraction with dichloromethane (3x10 mL) and usual work-up, the silyl ether **8b** (2.5 g, 88%) was recovered and used for the next step without purification. $\delta_H$ 0.0 (s, 6 H, $(CH_3)_2$Si, 0.90 (s, 9 H, $(CH_3)_3$C), 3.40 (s, 2 H, $CH_2$Ph), 4.10 (s, 2 H, $CH_2$O), 4.90 (s, 1 H, *CH*=), 5.20 (s, 1 H, *CH*=), 7.35 (m, 5 H, aromatic). The silyl ether **8b** (1.5 g, 5.7 mmol) was treated with ozone in three separated portions (0.5 g in 5.7 mL of dichloromethane) at -78 °C (7 min). The ozone excess was removed under a nitrogen stream and the collected dichloromethane solutions were added to a suspension of triphenylphosphine polymer bound[21] (1.89 g, 3 mmol/g) in dichloromethane (18 mL). After 2 h the solid was removed by filtration and the product recovered by evaporation of the solvent at reduced pressure (1.4 g, 93%). $\delta_H$ 0.0 (s, 6 H, $(CH_3)_2$Si, 0.90 (s, 9 H, $(CH_3)_3$C), 3.80 (s, 2 H, $CH_2$Ph), 4.25 (s, 2 H, $CH_2$O), 7.35 (m, 5 H, aromatic). To a solution of the ketone **9** (1.4 g, 5.3 mmol) in acetonitrile and dichloromethane (1:1, 21 mL) lithium fluoroborate (1.45 g, 15.46 mmol) was added. The reaction was kept at room temperature under stirring (15 h) and then a saturated sodium hydrogen carbonate was added to neutralize the mixture. After usual work-up, the hydroxy ketone **1d** (0.7 g, 88%) was recovered essentially pure. M. p. 47 °C (from dichloromethane/hexane); $\delta_H$ 3.40 (s, 1 H, exchangeable with $^2H_2O$), 3.60 (s, 2 H, $CH_2$Ph), 4.20 (s, 2 H, $CH_2$O), 7.35 (m, 5 H, aromatic). $C_9H_{10}O_2$: Anal. calc.: C, 71.98; H, 6.71. Found: C, 72.05; H, 6.80%.

***Acetate 3c.*** - To a solution of 4-bromophenacyl bromide (2.52 g, 9.0 mmol) in chloroform (25 mL), tetrabutylammonium acetate (3.4 g, 11.3 mmol) was added. After 3 h at room temperature water was added and the usual work-up afforded an oil that was purified by column chromatography (elution with hexane/ethyl acetate, 7:3). Yield: 1.6 g, 69%. $\delta_H$ 2.30 (s, 3 H, $CH_3$CO), 5.40 (s, 2 H, $CH_2$O), 7.70-8.15 (m, 4 H, aromatic).

***Acetate 3d.*** - To a solution of the hydroxy ketone **1d** (1.73 g, 11.5 mmol) in dry pyridine (4 mL), acetic anhydride (1.1 mL, 11.6 mmol) was added and the solution was kept overnight at room temperature. After work-up, the crude acetate **3d** was purified by column chromatography (elution with hexane/ethyl acetate, 9:1) affording pure **3d** (1.4 g, 63%). $\delta_H$ 2.10 (s, 3 H, $CH_3$CO), 3.80 (s, 2 H, $CH_2$Ph), 4.80 (s, 2 H, $CH_2$O), 7.40 (m, 5 H, aromatic).

***Methyl Ether 5a.*** - To a solution of potassium hydroxide (3.72 g, 66.5 mmol) in water (1.76 mL) styrene oxide (4 g, 33.3 mmol) in methanol (22.4 mL) was added at 0 °C and kept at room temperature for 8 h. The solution was neutralized with 1 N HCl and methanol removed at reduced pressure. After the usual work-up,

a 7:3 mixture of 1- and 2-monomethyl ethers was obtained, as shown by GLC chromatography on capillary column (HP 5, oven temperature 170 °C). Treatment of the above mixture in acetone (60 mL) with the Jones' reagent and work-up afforded a crude product, which was dissolved in dichloromethane (20 mL) and washed with saturated sodium hydrogen carbonate. Evaporation of the organic solvent gave the required methyl ether **5a** (2.14 g, 43% overall from styrene oxide); b. p. 200 °C (18 mm Hg). $\delta_H$ 3.55 (s, 3 H,$CH_3O$), 4.80 (s, 2 H, $CH_2O$), 7.35-7.85 (m, 3 H, aromatic), 7.85-8.30 (m, 2 H, aromatic). $C_9H_{10}O_2$: Anal. calc.: C, 71.98; H, 6.71. Found: C, 72.06; H, 6.78%.

***Methyl Ether 5d.*** - To a solution of allyl benzene (0.98 g, 8.31 mmol) in dichloromethane (12 mL), *meta*-chloroperbenzoic acid (containing 45% water, 3.20 g, 10 mmol) was added at room temperature. After 8 h, the precipitate was removed by filtration and the solution washed with 5% ammonium hydroxide and then water. Usual work-up afforded the essentially pure epoxide (0.6 g, 54%). $\delta_H$ 2.35-3.25 (m, 5 H, $CH_2$Ph, $CH_2O$, *CH*O), 7.20-7.45 (m, 5 H, aromatic). Opening of the epoxide and Jones' oxidation were carried out following the same previous protocol and afforded the title methyl ether **5d** (0.32 g, 22% from allyl benzene). $\delta_H$ 3.40 (s, 3 H, $CH_3O$), 3.75 (s, 2 H, $CH_2$Ph), 4.05 (s, 2 H, $CH_2O$), 7.15-7.60 (m, 5 H, aromatic). $C_{10}H_{12}O_2$: Anal. calc.: C, 73.15; H, 7.37. Found: C, 73.22; H, 7.45%.

***Methyl Ether 5b.*** - To a solution of 4-methoxy phenacyl bromide (2.5 g, 10.9 mmol) in absolute methanol (100 mL), freshly prepared sodium methoxide [from sodium (0.375 g, 16.30 mmol) in methanol (10 mL)] was added. The reaction was refluxed (1 h) then 1 N HCl was added to neutrality and methanol removed at reduced pressure. Extraction with dichloromethane (3x20 mL) and work-up afforded the crude product (1.9 g) that was purified by column chromatography. Elution with hexane/ethyl acetate (7:3) gave the title compound **5b** (1.7 g, 87%); m. p. 190-193 °C (from ethyl acetate). $\delta_H$ 3.55 (s, 3 H, $CH_3O$), 3.95 (s, 3 H, $CH_3O$), 4.75 (s, 2 H, $CH_2O$), 7.15 (d, 2 H, aromatic), 8.15 (d, 2 H, aromatic). $C_{10}H_{12}O_3$: Anal. calc.: C, 66.65; H, 6.71. Found: C, 66.72; H, 6.80%.

***Methyl Ether 5c.*** - Starting from 4-bromo phenacyl bromide, the procedure was as for the methyl ether **5b**, except that this bromide was added to the methanol solution of sodium methoxide to avoid side reactions. Yield: 38%; $\delta_H$ 3.50 (s, 3 H, $CH_3O$), 4.70 (s, 2 H, $CH_2O$), 7.70 (d, 2 H, aromatic), 7.95 (d, 2 H, aromatic). $C_9H_9O_2Br$: Anal. calc.: C, 47.19; H, 3.96. Found: C, 47.25; H, 4.05%.

***(R)-MTPA Esters of Optically Active Products.*** - Typically, a solution of the product (0.1 mmol) in a mixture of dry pyridine and carbon tetrachloride (0.5 mL, 1/1) was treated with (S)-MTPA chloride (0.12 mmol) at room temperature overnight. Then 3-dimethylamino-propylamine (21 μl) was added and after 10 min the mixture was treated with diethylether (0.5 mL). The solution was washed with 1N hydrochloric acid, saturated sodium hydrogencarbonate and sodium chloride solutions. After drying and evaporation of the solvents, the (R)-MTPA ester was recovered. The ee of the optically active compound was determined by the integrations of the signals of significant hydrogens in comparison with the racemic (R)-MTPA esters.

***Baker's Yeast-Mediated Reduction: General Procedure.*** - Typically, referring to 100 mL of water containing sucrose (6 g), a suspension of baker's yeast (12 g) was prepared and kept at 30 °C for 1 h. Then the substrate was added (ratio yeast/substrate indicated as g/mmol reported for single products) and the

mixture was kept at 30 °C under vigorous stirring. The progress of the reaction was monitored by TLC or GLC analysis. After disappearance of starting material, the mixture was filtered through a Celite pad and the aqueous phase was extracted with diethyl ether and the solvent was dried and evaporated to afford a crude mixture that was purified by column chromatography. The elution with the appropriate solvent mixture afforded the reduction products.

***(S)-(+)-1,2-Diol, 1-Acetate 4c.*** - Yeast/substrate, 1.8:1; TLC (toluene/ethyl acetate, 8:2). Yield: 34%; $\delta_H$ 2.10 (s, 3 H, $CH_3CO$), 2.85-3.10 (m, 1 H, exchangeable), 4.10-4.35 (m, 2 H, $CH_2O$), 4.90-5.15 (m, 1 H, *CH*O), 7.35 (d, 2 H, aromatic), 7.70 (d, 2 H, aromatic); $[\alpha]_D$ +21.8 (*c* 2 in acetone). A sample of (R)-(-)-**2c** prepared by BY reduction of the hydroxy ketone **1c** in 44% yield, $[\alpha]_D$ -33.5 (*c* 2 in acetone), was optically pure, as judged by the $^1$H-NMR (500 MHz) spectrum of its (R)-MTPA diester. The benzylic CH showed only a signal centered at 6.2 ppm, whereas the diester from the racemic **2c** gave two signals centered at 6.1 and 6.2 ppm. A sample of the (+)-**4c** was hydrolyzed (aq. $Na_2CO_3$ in methanol) to (+)-diol **2c**, $[\alpha]_D$ +28 (*c* 2 in acetone), corresponding to 84% ee.

***(R)-(-)-1,2-Diol, 1-Methyl Ether 6a.*** - Yeast/substrate, 5:1; TLC (toluene/ethyl acetate, 9:1); GLC: 150 °C. Yield: 35%; $\delta_H$ 2.80-3.00 (m, 1 H, exchangeable), 3.50-3.70 (m, 5 H, $CH_2O$ and $CH_3O$), 4.85-5.15 (m, 1 H, *CH*O), 7.30-7.70 (m, 5 H, aromatic). $[\alpha]_D$ -34.4 (*c* 2 in acetone).

***(R)-(-)-1,2-Diol, 1-Methyl Ether 6b.*** - Yeast/substrate, 22:1; TLC (chloroform/methanol, 9:1). Yield: 30%; $\delta_H$ 2.80-3.10 (m, 1 H, exchangeable), 3.40-3.65 (d+s, 5 H, $CH_2O$ and $CH_3O$), 3.90 (s, 3 H, $CH_3O$), 4.70-5.20 (m, 1 H, *CH*O), 7.05 (d, 2 H, aromatic), 7.50 (d, 2 H, aromatic). $[\alpha]_D$ -24.7 (*c* 2 in acetone).

***(R)-(-)-1,2-Diol, 1-Methyl Ether 6c.*** - Yeast/substrate, 2:1; TLC (toluene/ethyl acetate, 8:2). Yield: 26%; $\delta_H$ 2.60-3.10 (m, 1 H, exchangeable), 3.30-3.65 (m, 5 H, $CH_2O$ and $CH_3O$), 4.65-5.15 (m, 1 H, *CH*O), 7.35 (d, 2 H, aromatic), 7.65 (d, 2 H, aromatic). $[\alpha]_D$ -9.7 (*c* 2 in acetone).

***(R)-MTPA Esters of Optically Active Methyl Ethers.*** - The ee of the optically active compound was determined by the integrations of the benzylic hydrogens in comparison with the racemic (R)-MTPA esters. Racemic **6a**: two complex systems centered at 6.17 and 6.23 ppm; (R)-**6a**: two complex signals at the same values in a 12:88 ratio, 76% ee. Racemic **6b**: two complex systems centered at 6.12 and 6.17 ppm; (R)-**6b**: two complex signals at the same values in a 13:87 ratio, 74% ee. Racemic **6c**: two complex systems centered at 6.11 and 6.16 ppm; (R)-**6c**: two complex signals at the same values in a 18:82 ratio, 64% ee.

***Determination of the Absolute Configuration of the Methyl Ethers 6a and 6c: Synthesis of Dimethyl Ethers 7a and 7c.*** - Starting from optically active (R)-diols **2a** and **2c** (prepared *via* baker's yeast incubations), the (R)-dimethyl ethers **7a** and **7c** were prepared as reference standards. Typically, the (R)-diol (2 mmol) in tetrahydrofuran (8 mL) was added to a suspension of 90% sodium hydride (4.8 mmol) in tetrahydrofuran (10 mL). After 5 min, methyl iodide (0.5 ml, 8 mmol) was added and the mixture was kept at room temperature until disappearance of the starting material (ca. 3 h). The mixture was brought to neutrality by addition of 1 N HCl and then the solvent evaporated. The usual work-up afforded the required dimethyl ether which was purified by chromatography (hexane/ethyl acetate, 8:2). Similarly, from the optically active monomethyl ethers **6a** and **6c** obtained with fermenting baker's yeast, the corresponding dimethyl ethers were prepared in order to compare the optical rotations.

***(R)-(-)-Dimethyl Ether 7a.*** - Starting from (-)-**2a** with $[\alpha]_D$-37 (*c* 4.33 in ethanol), the compound **7a** was prepared (52%); $\delta_H$ 3.30-3.70 (m, 8 H, $CH_3O$ and $CH_2O$), 4.35-4.60 (m, 1 H, *CH*O), 7.35-7.65 (m, 5 H, aromatic); $[\alpha]_D$ -160 (c 0.63 in $CHCl_3$). The methyl ether (-)-**7a**, prepared from (-)-**6a** with $[\alpha]_D$-34.4 (*c* 2 in acetone), showed $[\alpha]_D$-130 (*c* 0.63 in chloroform).

***(R)-(-)-Dimethyl Ether 7c.*** - Starting from (-)-**2c** with $[\alpha]_D$-33.5 (*c* 2 in acetone), the compound **7c** was prepared (68%); $\delta_H$ 3.35 (s, 3 H, $CH_3O$), 3.45 (s, 3 H, $CH_3O$), 3.30-3.80 (m, 2 H, $CH_2O$), 4.30-4.65 (m, 1 H, *CH*O), 7.40 (d, 2 H, aromatic), 7.70 (d, 2 H, aromatic); $[\alpha]_D$ -15 (c 1 in acetone). The methyl ether (-)-**7c**, prepared from (-)-**6c** with $[\alpha]_D$-9.7 (*c* 2 in acetone), showed $[\alpha]_D$-9.7 (*c* 1 in acetone).

***Determination of the Absolute Configuration of the (-)-Monomethyl Ether 6b.*** - The direct reaction with equimolar amounts of sodium hydride and methyl iodide of the (R)-(-)-diol **2b** with $[\alpha]_D$ -35 (*c* 1 in ethanol) afforded the (R)-(-)-monomethyl ether **6b**. This was purified by column chromatography (28% yield), $[\alpha]_D$ -30 (*c* 2 in acetone). The monomethyl ether **6b** obtained *via* baker's yeast incubation of the methyl ether **5b** showed $[\alpha]_D$ -24 (*c* 2 in acetone) and therefore was in the R configuration.

***(R)-(+)-1,2-Diol 2d.*** - Yeast/substrate, 2:1; TLC (chloroform/methanol, 9:1). Yield: 58%; $\delta_H$ 2.75 (d, 2 H, $CH_2$Ph), 3.25-4.25 (m, 5 H, $CH_2O$, *CH*O, and two exchangeable hydrogens), 7.15-7.60 (m, 5 H, aromatic). $[\alpha]_D$ +23 (*c* 1.03 in chloroform) [lit.[22] -21.06 for the (S)-**2d**]. MTPA diester from racemic **2d**: eight double doublets between 4.10-4.70 ppm. From (R)-**2d**: double doublets centered at 4.54 and 4.62 ppm in 2.5:97.5 ratio (95%ee).

***(S)-(+)-1,2-Diol, 1-Acetate 4d.*** - Yeast/substrate, 1.6:1, incubation time 3 h; TLC (chloroform/methanol, 9:1); $[\alpha]_D$ +4.2 (*c* 1.03 in chloroform). The $^1$H-NMR spectrum (60 MHz) showed that the compound was the 1-acetate; $\delta_H$ 2.1 (s, 3 H, $CH_3O$), 2.70-3.05 (m, 3 H, $CH_2$Ph and exchangeable hydrogen), 3.90-4.30 (m + s, 3 H, *CH*OH and $CH_2$OCO), 7.20-7.70 (m, 5 H, aromatic). A sample (0.08 g, 0.4 mmol) was hydrolyzed ($LiAlH_4$) to the (S)-(-)-diol **2d**, $[\alpha]_D$ -15 (*c* 1.03 in chloroform) corresponding to 72% ee (from the MTPA-diester).

***(S)-(-)-1,2-Diol 2d.*** - Yeast/substrate, 1.6:1, incubation time 24 h; TLC (chloroform/methanol, 9:1). Yield: 25%; $[\alpha]_D$ -13 (*c* 1.03 in chloroform) corresponding to 60% ee (from the MTPA-diester).

***(R)-(+)-1,2-Diol, 1-Methyl Ether 6d.*** - Yeast/substrate, 20:1; TLC (toluene/ethyl acetate, 8:2). Yield: 20%; $\delta_H$ 2.75-3.05 (d+m, 3 H, $CH_2$Ph and exchangeable hydrogen), 3.30-3.65 (m, 5 H, $CH_2O$ and $CH_3O$) 3.85-4.40 (m, 1 H, *CH*O), 7.30-7.55 (m, 5 H, aromatic). $[\alpha]_D$ +0.3 (*c* 1.03 in chloroform). MTPA ester from racemic **6d**: one doublet centered at 2.89 ppm and a complex system constituted by eight signals between 2.90 and 3.05 ppm. (R)-**6d**: a 14:86 ratio between the doublet and the complex, 72% ee.

***Determination of the Absolute Configuration of the Methyl Ether 6d.*** -

Starting from optically active (R)-diol **2d** (prepared *via* baker's yeast incubation), the (R)-dimethyl ether **10** was prepared as previously described for methyl ethers **7a** and **7c**. From the optically active monomethyl ether **6d** obtained with fermenting baker's yeast, the corresponding dimethyl ether **10** was prepared in order to compare the optical rotations. Starting from (+)-**2d** with $[\alpha]_D$+23 (*c* 1.03 in chloroform) the compound **10** (50%); $\delta_H$ 2.75-3.10 (m, 2 H, $CH_2$Ph), 3.30-3.70 (two singlets + a multiplet, 9 H, $CH_3O$, $CH_2O$ and *CH*O), 7.30-7.55 (m, 5 H, aromatic); $[\alpha]_D$ -3.5 (*c* 1.03 in chloroform). (-)-**10** prepared from (+)-**6d** with $[\alpha]_D$+0.3 (*c* 1.03 in chloroform) showed $[\alpha]_D$-2.7 (*c* 1.03 in chloroform).

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***References and Notes***

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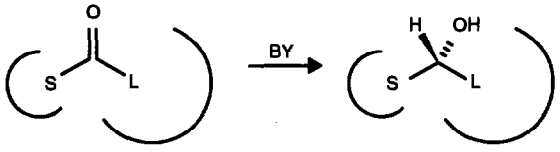


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