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MICROBIAL REDUCTION OF 2-KETO ACETALS AS A BIOCATALYTIC APPROACH TO THE ENANTIOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE 2-HYDROXY ACETALS

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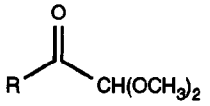
Abstract. - The reduction of the 2-keto acetals **1a** and **1b** by means of different microorganisms constitutes the biocatalytic access to optically active (46 to 100% ee) 2-hydroxy acetals, (S)-**2a** or (R)- and (S)-**2b**, representative compounds of a class of synthetically useful chiral building blocks.

Introduction

Enantiomerically pure α and β-hydroxy aldehydes can be useful chiral synthons for the preparation, for instance, of a few natural products,[1] including arachidonic acid metabolites[2] and prostaglandin E_2.[3] The biocatalytic approach to the preparation of these compounds include the microbial reduction of the corresponding α and β-keto thioacetals[4] and the enzymatic resolution of the racemic hydroxy aldehydes.[5] 2-Keto acetals can also be considered good precursors for optically active α-hydroxy aldehydes synthesis, but their preparation often requires several steps. Recently, some simple procedures based on organoselenium intermediates have been proposed in the literature.[6,7] In these works, methyl ketones or terminal alkynes are reacted with catalytic or stoichiometric amounts of diphenyl diselenide and an excess of ammonium peroxydisulfate in boiling methanol. The corresponding α-keto dimethyl acetals are obtained in good isolated yields. We decided to explore the microbial reduction of these compounds which could constitute a feasible biocatalytic access to enantiomerically pure protected hydroxy aldehydes.



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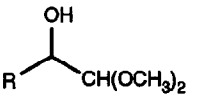


2

a. R = Ph b. R = C_4H_9

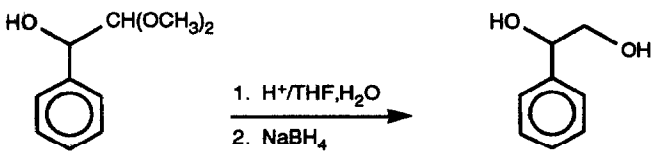
The 2-keto acetals **1a** and **1b** were chosen as model compounds, representative of aromatic and aliphatic substrates, and were synthesized starting from acetophenone[6] and 1-hexyne,[7] respectively. The reduction to the corresponding hydroxy compounds **2a** and **2b** was at first attempted with *Saccharomyces cerevisiae* (baker's yeast), a microorganism which can actually be considered like a reagent for asymmetric organic synthesis.[8]

Baker's Yeast Mediated Reduction of 2-Keto acetals 1a and 1b

Fermenting baker's yeast was able to reduce both substrates **1a** and **1b** within 40 and 90 hours, respectively. The ratio yeast/keto acetal was 10 g/mmol and the reduction of the aliphatic **1b** required longer reaction time and additional fermenting yeast (50%). Yields were higher for the aromatic substrate **1a** (45% of isolated **2a**) than for **1b** (26% of **2b**). The ee of (+)-**2a** and (-)-**2b** was 46 and 60%, respectively, as estimated by 500 MHz ^{1}H-NMR of the corresponding Mosher ester.[9] It should be noticed that the ee of **2a** could be raised to 60%, carrying out the incubations under anaerobic conditions. The optical rotations of the above hydroxy acetals were not found in the literature, so it became compulsory to determine the absolute configuration of both **2a** and **2b**. The work was first carried out on the racemic hydroxy acetals, which were easily prepared from the corresponding keto acetals **1a** and **1b** by sodium borohydride reduction (80-90% yield).

Determination of the Absolute Configuration of the Hydroxy acetal 2a

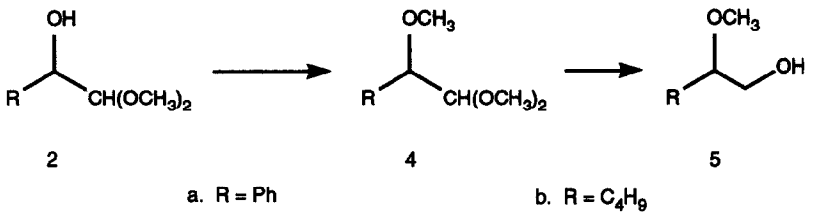
Initially, we decided to convert **2a** into the known 2-phenylethane-1,2-diol **3**,[10] by an acidic hydrolysis of the acetal moiety of **2a**. Addition of sodium hydroxide and reduction *in situ* of the intermediate aldehyde by means of sodium borohydride afforded the diol **3** from **2a** in 20% (Scheme 1).



2a 3

Scheme 1

However, from optically active (+)-**2a** (46% ee) the racemic diol **3** was obtained. We decided to protect the hydroxy group of the compound **2a**, which, according to Scheme 2, was converted into the 2-methoxy ether **4a** (NaH, CH_3I in THF, 93% yield). Hydrolysis of the acetal group in compound **4a** (3N HCl in THF), followed by addition of 3N NaOH to pH 9, and $NaBH_4$ reduction of the intermediate methoxy aldehyde afforded the methoxy diol **5a** in 22% yield.

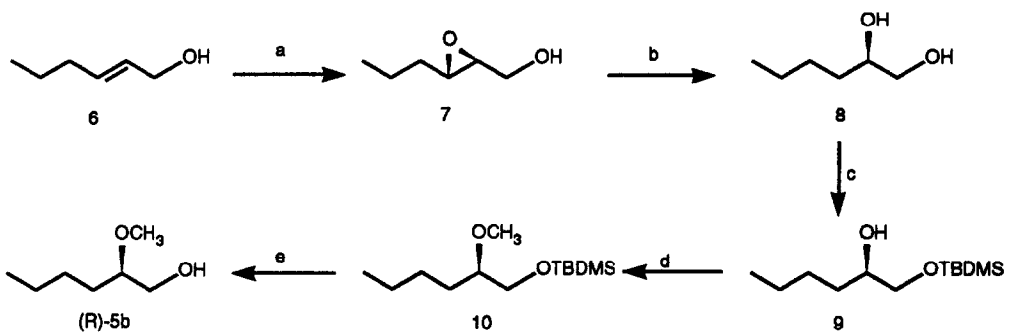


Scheme 2

Repetition of this procedure from 46% ee (+)-**2a** gave (S)-(+)-**5a**[11] with 13% ee, consistent with an extensive racemization which had occurred also on the intermediate methoxy aldehyde. However, the optical rotation of the sample obtained allowed us to establish that the baker's yeast reduction of the keto acetal **1a** had afforded the (S)-(+)-**2a**.

Determination of the Absolute Configuration of the Hydroxy acetal 2b

In this case, we repeated the synthetic sequence outlined in the Scheme 2 and prepared the methoxy diol **5b**, starting from the 60% ee hydroxy acetal (-)-**2b**. This sample was converted into the methyl ether **4b**, which was directly hydrolyzed and reduced to the protected diol (-)-**5b**. A sample of this compound (-)-**5b** exhibited an optical rotation of -1.56 and should be correlated to a reference compound, which was prepared from the optically active diol **8**.[12] We prepared a sample of (R)-(+)-diol **8** starting from commercial *trans* 2-hexenol **6** (Scheme 3).



Scheme 3

A Sharpless asymmetric epoxidation with L-(+)-tartrate[13] afforded the (2S,3S)-epoxy alcohol **7** (90% ee), which was regioselectively reduced by diisobutyl aluminum hydride (DIBAL)[14] to the 1,2-diol (R)-**8**. For a selective preparation of the 2-methyl ether we preferred to protect the primary alcohol as *tert*-butyldimethylsilyl ether.[15] The methylation of the silyl ether **9** was carried out as previously described and the silyl group of the compound **10** was removed with lithium tetrafluoborate[16] to afford the (R)-methyl ether **5b**, $[\alpha]_D$+1.8. Since a methoxy ether (-)-**5b** was obtained from (-)-**2b**, this establishes that baker's yeast reduction yields (S)-(-)-**2b**.

Microbial Reductions of 2-Keto acetals 1a and 1b

Using baker's yeast as reducing agent, yield and enantioselectivity are only moderate and these results led us to investigate the biorecduction of the substrates **1a** and **1b** by other microbial whole cells. While no significant reduction could be observed with various lactic acid bacteria capable to reduce ketones,[17] a few yeasts resulted effective in promoting the reaction with different yields and stereochemical outcomes. The configurations and optical purities were established by capillary GC and as standards, the MTPA esters of the (S)-hydroxy acetals **2a** and **2b** obtained with baker's yeast were used. The results of this screening test (substrate concentrations of 2 g/l) are reported in the Table.

Bioreduction of alcohols 2a and 2b with different yeasts

		Alcohol **2a**		Alcohol **2b**	
	Microorganisms[a]	yield (48 h)	e.e.[b]	yield (48 h)	e.e.
1	baker's yeast	45%	46%	26%	60% (S)
2	*Hansenula glucozyma* CBS 5766	100%	60%	100%	94% (S)
3	*Kloeckera saturnus* MIM	30%	90%	46%	92% (S)
4	*Sporobolomyces salmonicolor* MAT MM	18%	84%	40%	64% (S)
5	*Hansenula anomala* MAP 2873	5%	not recorded	9%	88% (S)
6	*Sporobolomyces alborubescens* CBS 482	no reaction		15%	94% (S)
7	*Kluyveromyces fragilis* CBS 397	no reaction		18%	100% (R)
8	*Kluyveromyces marxianus* CBS 1553	53%	92%	60%	100% (R)
9	*Kluyveromyces marxianus* MIM 287	30%	100%	80%	80% (R)
10	*Hansenula minuta* CBS 1708	100%	96%	50%	20% (R)
11	*Rhodotorula minuta* var. *texensis* CBS 2177	3%	not recorded	18%	76% (R)

[a]Abbreviations **MIM**, Microbologia Industriale, Milano. **CBS**, Centraalbureau voor Schimmelcultures, Baarn. **MAT**, Microbiologia Agraria, Torino. **MAP**, Microbiologia Agraria, Perugia.
[b]Prevalent S configuration with all the strains.

Quantitative reduction of the keto acetal **1a** was achieved using *Hansenula minuta* CBS 1708 and *Hansenula glucozyma* CBS 5766, the latter being capable also to quantitatively reduce the ketoacetal **1b**. The aromatic alcohol **2a** was formed with prevalent *S* configuration with all the strains, and this result is in agreement with the stereochemical outcome of the baker's yeast reduction. This can be tentatively ascribed to the fact that for the examined microorganims, the difference in size between the phenyl and the acetal group influences the stereobias of the hydride attack. The bioreduction of the aliphatic keto acetal **1b** proceeds in a different mode, since both enantiomers of the aliphatic alcohol **2b** were obtained with good to excellent ee. For the two enantiomeric alcohols **2b**, the best ee was 94% for (S)-**2b** (*Hansenula glucozyma* CBS 5766 and *Sporobolomyces alborubescens* CBS 482) and 100% for (R)-**2b** (*Kluyveromyces marxianus* CBS 1553 and *Kluyveromyces marxianus* CBS 397). Additionally, in order to obtain the two enantiomers of **2b** on a larger scale, semi-preparative productions were carried out. The 2-keto acetal **1b** (0.5 g) was tranformed at a the concentration of 2 g/l in two experiments using *Hansenula glucozyma* CBS 5766 or *Kluyveromyces marxianus* CBS 1553 (Fig.1).

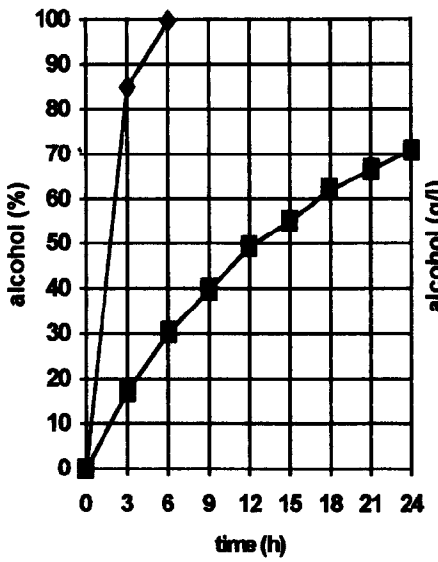


Figure 1. Production of the alcohol **2b** by *H. glucozyma* (◆) and *K. marxianus* (■) at 2 g/l substrate concentration.

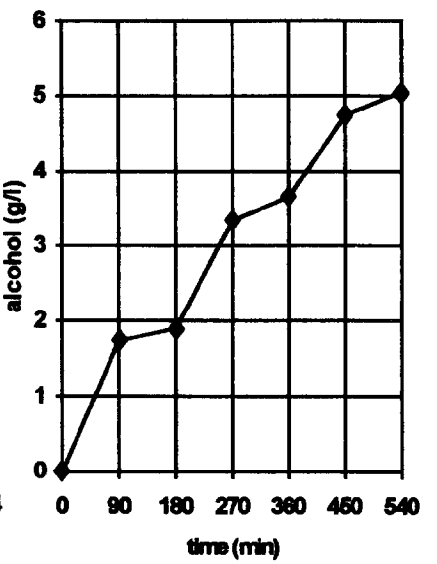
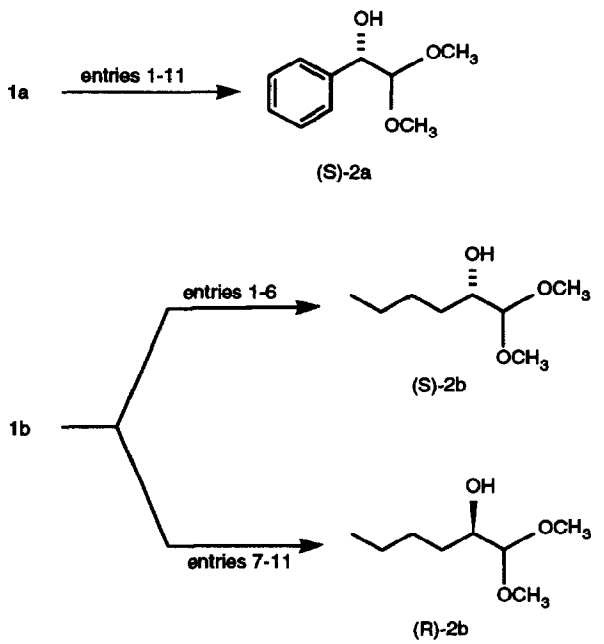


Figure 2. Production of the alcohol **2b** by *H. glucozyma* with semi-continuous addition of substrate (2 g/l after 3 and 6 hours).

Complete transformations were achieved in both cases and slightly lower ee were obtained in these scaled-up transformations [87% ee for (S)-**2b** with *Hansenula glucozyma* CBS 5766 and 94% ee for (R)-**2b** with *Kluyveromyces marxianus* CBS 1553]. The fast and quantitative reduction obtained by *Hansenula glucozyma* CBS 5766 led us to perform this transformation in a semi-continuous mode (Fig. 2). After 3 hours and 96% conversion, 2 g/l of substrate were added to the reaction mixture and a similar rate of alcohol production was observed. Another addition of the same amount of substrate after 6 hours showed only a small decrease in the formation rate of the product **2b**.

Conclusions

We have shown that the baker's yeast-mediated bioreduction of the two 2-keto acetals **1a** and **1b**, chosen as model compounds, proceeds with moderate yield and enantioselectivity. In both cases a 2-hydroxy acetal with the S configuration is obtained, in agreement with the Prelog' rule[18] if it is assumed that the dimethoxy acetal is the relatively large (L) group and the phenyl and butyl groups behave as small (S) substituents.[19] The above microbial synthesis of optically active **2a** and **2b** was useful also for the preparation of standard diastereomeric MTPA esters for the gas chromatographic determination of the ee and configuration of the biotransformation products by other microorganisms. The yeasts examined allowed a preparation of up to 100% ee of (S)-**2a** and a homogeneous stereochemical course was observed. For the aliphatic substrate **1b** the stereochemistry depends on the microorganism, so that, by the judicious choice of the biocatalyst, an easy and convenient preparation of both enantiomers of **2b** becomes available and in best cases optically pure **2b** can be prepared (Scheme 4).



Entries 1-11 refer to the Table

Scheme 4

Further, semi-preparative productions of the (R) and (S)-**2b** are feasible in 94 and 87% ee, with *Kluyveromyces marxianus* CBS 1553 and *Hansenula glucozyma* CBS 5766, respectively. In the case of *Hansenula glucozyma* CBS 5766, this was also accomplished in a semi-continuous mode. This investigation seems quite promising and could lead to pratical applications, adding important informations to the growing field of the biocatalytic access to enantiomerically pure chiral synthons.[18]

Experimental Section

Solvents and reagents were purchased from Fluka (Switzerland); sodium hydride was available from Aldrich (U.S.A.) as powder (dry, 97% purity). The substrates **1a** and **1b** were synthetized according to Ref. 6 and 7. The source of the microorganisms is indicated in the Table. 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 $SiMe_3$ 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 either on silica gel Merck 60 (230-400) or aluminum oxide (Merck, activity stage III). Gas chromatographic analyses of the microbial substrates and products were performed on a Carlo Erba Fractovap 2150 equipped with a hydrogen flame ionization detector on a 4 x 1,500 mm column packed with Carbowax 1,500 (10% on Chromosorb W 80-100 mesh, Carlo Erba, Italy), column temperature at 100 °C. The ee was determined by analysis of the MTPA esters, prepared according to the Mosher method (Ref. 9) by reaction of the alcohols with (S)-(+)-α-methoxy-α-trifluoromethyl phenylacetyl chloride. Gas chromatographic analyses were performed on a capillary column (SE 52, Carlo Erba, Italy) at 150 °C. 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.

Baker's yeast Mediated Reduction: General Procedure. - A suspension of baker's yeast (100 g) in a solution containing sucrose (50 g) in water (850 mL) was kept at 30 °C for 1 h. Then the keto acetal (10 mmol) was added and the mixture was kept at 30 °C under vigorous stirring. The progress of the reaction was monitored by TLC analysis (toluene/ethyl acetate, 9/1). An additional amount of fermenting baker yeast was added after 24 h in the case of 1,1-dimethoxy-2-hexanone **1b** [50 g of yeast in a solution containing sucrose (25 g) in water (425 mL)]. The reaction was worked-up after 90h for the compound **1b** and after 40 h for the compound **1a**. The mixture was filtered through a Celite pad and the aqueous phase was extracted with diethyl ether (4x500 mL) and the solvent was dried and evaporated to afford a crude mixture that was purified by column chromatography on neutral aluminum oxide. The fractions eluted with hexane/ethyl acetate (9:1) afforded the reduction products.

(+)-2-Hydroxy acetal 2a: Yield, 45%; b.p. 243-245°C (760 mm Hg); δ_H 3.15 (s, 3 H, O*CH*$_3$), 3.35 (s, 3 H, O*CH*$_3$), 4.20 (d, 1 H, *CH*OH), 4.60 (d, 1 H, OCHO), 4.20-4.60 (m, 1 H, exchangeable with ^2H_2O), 7.20-7.65 (m, 5 H, aromatic); $[\alpha]_D$ +4.72 (*c* 5 in $CHCl_3$). $C_{10}H_{14}O_3$: Anal. calc.: C, 65.92; H, 7.74. Found: C, 66.0; H, 7.92%. When the incubations were performed under anaerobic conditions (under nitrogen), a sample of compound **2a** was obtained with an optical rotation of +5.6.

(-)-2-Hydroxy acetal 2b: Yield, 26%; b.p. 135-140 °C (760 mm Hg); δ_H 0.9 (t,3 H, *CH*$_3$), 1.2-1.6 (m, 7 H, *CH*$_2$ and H exchangeable with ^2H_2O), 3.3-3.6 (m, 7 H, O*CH*$_3$ and *CH*O), 4.2 (d, 1 H, O*CH*O); $[\alpha]_D$ -19 (*c* 1 in CH_2Cl_2). $C_8H_{18}O_3$: Anal. calc.: C, 59.23; H, 11.18. Found: C, 59.32; H, 11.25%.

(R)-MTPA Esters of Hydroxy acetals 2a and 2b. - A solution of the hydroxy acetal (0.36 mmol) in a mixture of dry pyridine and carbon tetrachloride (2 mL, 1/1) was treated with (S)-MTPA chloride (0.44 mmol) at room temperature overnight. Then 3-dimethylamino-propylamine (75 µl) was added and after 10 min the mixture was treated with diethylether (2 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 compound **2a** was determined by the integrations of the signal due to the benzylic proton. The two doublets at

5.98 and 6.05 ppm were in a ratio 27/73 corresponding to a 46% ee. In the case of the compound **2b**, the signal due to the C-1 proton showed two doublets in a ratio 20/80 at 4.25 and 4.34 ppm corresponding to a 60% ee.

Determination of the Absolute Configuration of the (+)-Hydroxy acetal 2a

(S)-(+)-2-Phenyl-2-methoxy ethanol 5a. 0.5 g (2.75 mmol) of the (+)-**2a** prepared as above, in dry tetrahydrofuran (5 mL) were added to a suspension of 90% sodium hydride (0.29 g, 11 mmol) in tetrahydrofuran at room temperature. After 5 min, methyl iodide (0.205 mL, 3.29 mmol) was added. The progress of the reaction was monitored by TLC (toluene/ethyl acetate, 9/1) until disappearance of the starting material. After addition of water, the solution was neutralized with 3N hydrochloric acid and the tetrahydrofuran evaporated at reduced pressure. Extraction with diethyl ether, drying and evaporation of the solvent, afforded the methyl ether (0.5 g, 93%) that was used without purification for the next step. The acetal was removed by hydrolysis with 3N HCl (4 mL) in tetrahydrofuran (4 mL). After 3-4 h, the pH was brought to 9 with 3N NaOH and $NaBH_4$ (0.270 g, 7 mmol) was added. The reaction was kept at room temperature for 3h. After neutralization with 3N HCl, the organic solvent was evaporated at reduced pressure and the aqueous phase extracted with dichloromethane (3x5 mL). The usual work-up afforded the crude 2-phenyl-2-methoxy ethanol **5a** (0.087 g, 22%) which was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3 as eluant). The chemico-physical properties of (S)-**5a** were in agreement with literature data.[11] $[\alpha]_D$ +16 (c 2.23 ethanol) [lit. -127 for (R)-**5a**].

Determination of the Absolute Configuration of the (-)-Hydroxy acetal 2b.

(S)-(-)-1,2-Hexanediol, 2-methyl ether 5b from (-)-2b. This compound was prepared from the compound **2b** obtained by the *Saccharomyces cerevisiae* mediated reduction. Thus, the (-)-hydroxy acetal **2b** (0.28 g, 1.7 mmol) in tetrahydrofuran (4 mL) was added to a suspension of 90% sodium hydride (0.045 g, 1.7 mmol) in tetrahydrofuran (4 mL). After 5 min, methyl iodide (0.126 ml, 20 mmol) was added and the mixture was kept at rooom temperature until disappareance of the starting material. The usual work-up afforded the required methyl ether which was purified by chromatography on neutral aluminum oxide (0.185 g, 62%); b.p. 100°C (760 mmHg); $C_9H_{20}O_3$: Anal. calc.: C, 61.33; H, 11.44. Found: C, 61.42; H, 11.53%. δ_H 0.9 (t, 3 H, CH_3), 1.1-1.7 (m, 6 H, CH_2), 3.5-3.7 (m, 9 H, O*CH3*), 3.7-4.0 (m, 1 H, O*CH*), 4.35 (d, 1 H, OCHO); $[\alpha]_D$ -13.7 (*c* 5 in $CHCl_3$). Acidic hydrolysis (1N HCl in tetrahydrofuran, as for **2a**) followed by sodium borohydride reduction afforded (-)-1,2-hexanediol, 2-methyl ether **5b** (0.058 g, 42%); b.p. 125 °C (760 mmHg); $C_7H_{16}O_2$ Anal. calc.: C, 63.59; H, 12.20. Found: C, 63.71; H, 12.30%. δ 0.9 (t, 3 H, CH_3), 1.1-1.7 (m, 6 H, CH_2), 2.8-3.0 (m, 1 H exchangeable with ^2H_2O), 3.3-3.7 (m+s, 4 H,CHO and OCH_3); $[\alpha]_D$ -1.56 (*c* 2.23 in ethanol). The optical purity of this product was determined by the 500 MHz ^{1}H-NMR analysis of its (R)-MTPA ester. In the spectrum of the derivative from the racemic compound, the signals due to the C-2 hydrogens were six doublets between 4.22 and 4.40 ppm, simplified to three doublets by irradiation of the signal of the C-1 hydrogen. The spectrum from the (-)-hydroxy acetal **2a** showed the doublets at 4.35 and 4.38 ppm in a ratio 80/20, corresponding to a 60% ee, as for the starting material.

Chemical Synthesis of (R)-(+)-1,2-Hexanediol, 2-methyl ether 5b. The reference optically active compound **5b** was prepared from (R)-1,2-hexanediol **8**, in turn prepared *via* the Sharpless asymmetric epoxidation of commercial *trans*-hexenol **6** and regioselective (DBAL) reduction of 2,3-epoxy-1-hexanol **7**.

(R)-(+)-1,2-Hexanediol 8. A solution of titanium isopropoxide (5.9 mL, 21.5 mmol) and dimethyl L-(+)-tartrate (3.4 mL, 23.6 mmol) in dry dichloromethane (200 mL), under nitrogen at -23 °C, was treated with *ter*-butylhydroperoxide (5 mL of a 80% solution in di-*ter*-butylhydroperoxide, 40 mmol). *trans*-Hexenol **6** (2 g, 20 mmol) was added and the resulting mixture was kept at -23 °C overnight. After adddition of a 10% solution of (L)-tartaric acid (50 mL), the mixture was stirred for 0.5 h at -23°C and for 1h at room temperature. The organic phase was washed with water and the work-up afforded an oil that was dissolved with diethyl ether (150 mL) and after cooling at 0 °C, treated with 1N sodium hydroxyde (60 mL) for 0.5 h. The crude mixture from the work-up was purified by chromatography (silica gel). Using hexane/ethyl acetate 6/4 as eluant, the required epoxide **7** was obtained (0.9 g, 39%). To a solution of the above epoxyalcohol **7** (0.3 g, 2.58 mmol) in dry tetrahydrofuran (20 mL) under nitrogen, diisobutyl aluminum hydride (DIBAL, 1M in hexane, 3.9 mL) was added. The reaction was kept at room temperature for 3 h and 10% sulphuric acid was added (pH 2-3). After neutralization with a saturated solution of sodium hydrogencarbonate, the organic solvent was removed. The crude product was recovered by extraction with diethyl ether and usual work-up. After column chromatography (silica gel, dichloromethane/methanol, 95/5 as eluant), the required (R)-diol **8** was recoverd in 52% yield (0.16 g) and presented chemico-physical properties in full agreement with literature data.[12]

(R)-(+)-1,2-Hexanediol, 2-methyl ether 5b. The diol **8** (0.16 g, 1.35 mmol) was dissolved in pyridine (0.5 mL) and *ter*-butyldimethylsilyl chloride (0.203 g, 1.35 mmol) was added. The solution was kept at room temperature overnight and, at the end of the reaction, water (1 mL) was added. Extraction with dichloromethane (3x20 mL) afforded the silyl ether **9** (0.36 g) that was used without purification. The crude product was dissolved in dry tetrahydrofuran (3 mL) and added to a suspension of sodium hydride (90% in oil, 0.036 g, 1.3 mmol) in tetrahydrofuran (1 mL). Methyl iodide (0.1 mL, 1.6 mmol) was added and after the work-up described for the compound **5a**, the compound **10** was recovered by silica gel column chromatography (hexane/ethyl acetate, 9/1 as eluant) (0.172 g, 52% from the diol **8**); b.p. 152 °C (760 mm Hg); δ_H 0.0 (s, 6 H, CH_3Si), 1.85 (s,12 H, CH_3), 1.1-1.7 (m, 6 H, CH_2), 3.2-3.7 (m, 6 H, CH_3O, CH_2O and CHO). $C_{13}H_{30}O_2Si$:Anal. calc.: C, 63.35; H, 12.27. Found: C, 63.42; H, 12.35%. The compound **10** (0.172 g, 0.7 mmol) was treated overnight at room temperature with lithium tetrafluoborate (0.2 g, 2.1 mmol) in a mixture of acetonitrile/dichloromethane (1/1, 6 mL). After washing with saturated sodium hydrogencarbonate, usual work-up and purification by silica gel chromatography, the required (R)-1,2-hexanediol,2-methylether **5b** (0.06 g, 65%) was obtained. $[\alpha]_D$ +1.8 (*c* 2.23 in ethanol). The other chemico-physical properties were as for the (S)-1,2-hexanediol, 2-methylether **5b** prepared from the optically active hydroxy acetal **2b** obtained by baker's yeast mediated reduction; $[\alpha]_D$ -1.56 (*c* 2.23 in ethanol)

Microbiological Reductions: General Procedure. - All the microorganisms were cultured in shaking flasks (750 mL) with 100 mL of growth medium containing 2% glucose, 0.5% ammonium sulfate,

0.1% K_2HPO_4, 0.1% yeast extract and 0.01% magnesium sulfate, pH 5.8. The cultures were incubated for 24 h on a reciprocating shaker (100 strokes/min) at 28 °C. The reductions were carried out using resting cells. Fresh cells from submerged cultures were collected by centrifugation and resuspended (ca. 30 mg dry weight cells/mL) in 0.2 M sodium phosphate buffer (pH 6.8) in the presence of 10% glucose. 10 mL of this suspension were withdrawn and placed in 50 mL shaking flasks and 1 mL of a solution of the substrate in acetone (20 g/l) was added. The resulting mixture was left at 28 °C on a reciprocating shaker. Larger scale transformations were performed in 1 l shaking flasks, adding 0.5 g of the substrate solution in acetone to 250 mL of the previous cell suspension at the same temperature on a reciprocating shaker (100 spm). At the end of the transformation, a 0.05% NaCl solution was added and the reaction mixture extracted with diethyl ether.

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