Chemistry of Natural Compounds and Bioorganic Chemistry

A chemo-enzymatic approach to optically active 3-(4-methoxycarbonyl)phenyl-2-methyl-1-propanols

G. D. Gamalevich, A. V. Ignatenko, E. P. Serebryakov, and N. E. Voishvillo*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

With a view to obtaining both enantiomers of 3-(4-methoxycarbonyl)phenyl-2-methyl-1-propanols, (*R*)-**1** and (*S*)-**1**, from the respective racemate, (±)-**1**, the hydrolysis of its acetate, (±)-**2**, in the presence of porcine pancreatic lipase (PPL) has been studied. The optical puriry of (*R*)-**1** and (*S*)-**1** thus obtained was unsatisfactory (*ee* 22—27 %), and could not be increased beyond *ee* 33 % by repeated enzymatic hydrolysis of the unconverted fraction of the acetate. In contrast with this, the biohydrogenation of 3-(4-methoxycarbonyl)phenyl-2-methyl-2-propen-1-ol (**4**) with fermenting *Saccharomyces cerevisiae* afforded (*S*)-**1** of considerably higher optical purity (*ee* 41—90 %, depending on the strain). The stereochemical correlation of the products obtained in the two biochemical processes under study shows that the PPL-catalyzed hydrolysis of (±)-**2** produces preferably (*R*)-**1**.

Key words: pancreatic lipase; (±)-3-(4-methoxycarbonyl)phenyl-2-methylprop-1-yl acetate, enzymatic hydrolysis; 3-(4-methoxycarbonyl)phenyl-2-methyl-2-propen-1-ol, yeast reduction.

Recently, an expedient synthesis of 4-(2,6-dimethyl)heptylbenzoic acid, an efficient inhibitor of the biosynthesis of cholesterol both in rats[1] and in human aortic cell culture,[2] was designed and carried out in our laboratory.[2] Since the molecule of this inhibitor contains a stereogenic center in the side chain, both enantiomers of the acid are necessary for comparative biomedical studies. For this purpose we tested the feasibility of the optical resolution of racemic 3-(4-methoxycarbonyl)phenyl-2-methyl-1-propanol, (±)-**1**, by the enzymatic hydrolysis of its acetate, (±)-**2**. Successful implementation of this straightforward procedure could afford both enantiomers of the target alcohol in only three steps.

Aldehyde **3**, a convenient precursor of (±)-**1**, was easily prepared according to a recent procedure.[3] It was

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 761—766, April, 1995.

1066-5285/95/4404-0743 $12.50

smoothly reduced to the corresponding allylic alcohol (**4**) which was converted to (±)-**1** by catalytic hydrogenation. Acetylation of (±)-**1** afforded the racemic acetate, (±)-**2**. Porcine pancreatic lipase (PPL), an inexpensive, commercially available enzyme with a good record of enantioselectivity in solvolytic reactions,[4–7] was used for the hydrolysis of (±)-**2**. The latter was partially hydrolyzed in the presence of PPL (substrate : enzyme = 2 : 1; 50 % conversion) to give the dextrorotatory alcohol (in 67 % yield) and a dextrorotatory residual acetate (80 % recovery). The unconverted acetate was deacetylated with NaOMe in anhydrous MeOH to afford the levorotatory stereoisomer of the alcohol. Both the dextro- and levorotatory alcohols were transformed to the respective esters of the (*S*) Mosher's acid [(*S*)-(−)-MTPA esters], tentatively designated as (*R*)-**5a** and (*S*)-**5a**. The enantiomeric purity of the thus derivatized alcohol was assessed by a known technique[8] using ^{19}F NMR spectroscopy, and was equally low for both the dextrorotatory ($[\alpha]_D^{22}$ +2.16°) and the levorotatory alcohol (*ee* 22.2 and 23.0 %, respectively). An attempt to enhance the enantioselectivity of hydrolysis by raising the substrate-to-enzyme ratio to 10 : 1 (w/w) and arresting the hydrolysis at a somewhat lower conversion (43±2 %) proved unsuccessful: the *ee* of the dextrorotatory alcohol remained as low as 27 %.

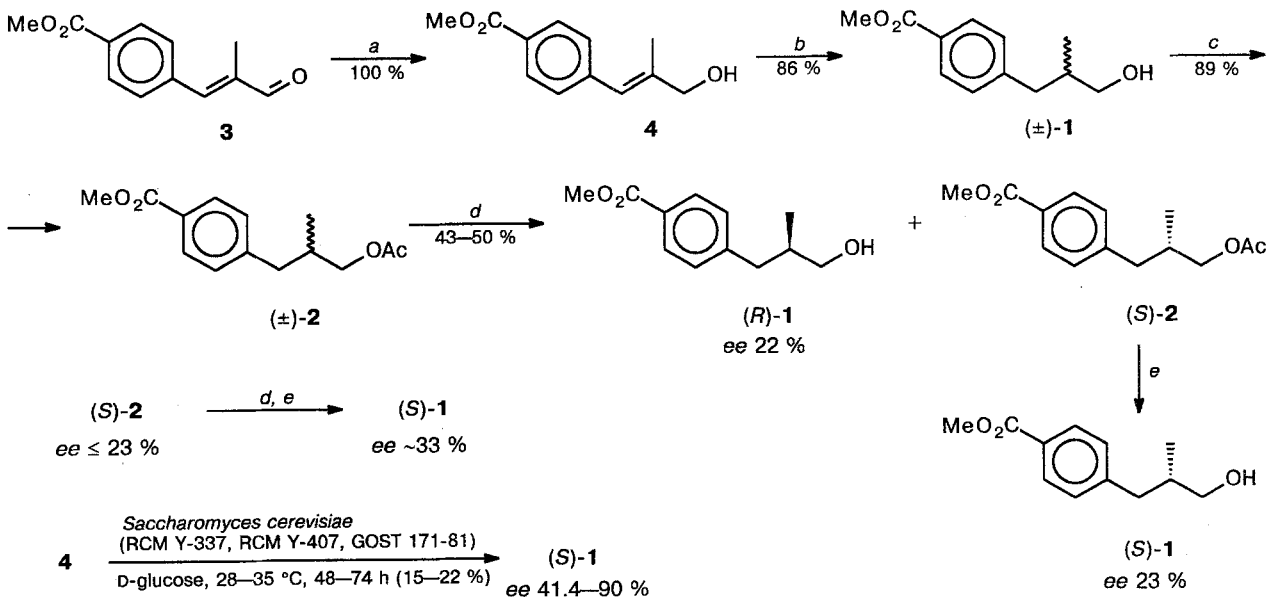
When the acetate fraction recovered after 43 % conversion of (±)-**2** was resubjected to PPL-catalyzed hydrolysis (substrate : enzyme = 10 : 1, conversion 44±2 %) and the recovered acetate was treated with MeONa in MeOH, a specimen of the levorotatory alcohol was obtained ($[\alpha]_D^{23}$ −3.39°, in $CHCl_3$) with *ca* 30 % *ee* according to the signal intensity ratio in the ^{19}F NMR spectrum of its (*S*)-MTPA ester (Scheme 1).

Since various 3-carbo-substituted 2-methyl-1-propanols with alkyl,[9,10] alkenyl,[11–12] aryl,[13] and heteroaryl substituents[10,14] are levorotatory in the case of the 2*S* configuration, our levorotatory alcohol was assumed to be (*S*)-**1**, and its dextrorotatory counterpart was tentatively denoted as (*R*)-**1**.

This assignment was confirmed by the reduction of allylic alcohol **4** with bakers' yeast (B.Y.).* The biohydrogenation of the double bond in various 3-substituted 2-methylpropenals and/or in the respective 3-substituted 2-methyl-2-propen-1-ols by B.Y. is known to produce the *S* enantiomers of the corresponding 3-substituted 2-methyl-1-propanols with high enantioselectivity.[9–14] When treated with *Saccharomyces*

* When aldehyde **3** was used as the substrate the growth of the biomass was markedly suppressed (by 25—30 %), and the conversion of **3** was low and gave rise mainly to alcohol **4**.

Scheme 1



Reagents and conditions: *a*. $NaBH_4$/MeOH, −5 °C; *b*. H_2—Pt (C)/MeOH, 20—22 °C, 1 atm; *c*. Ac_2O—Py, 20—22 °C; *d*. PPL/H_2O (pH 6.5), 20—22 °C, then column chromatography (SiO_2); *e*. NaOMe—MeOH, 20—22 °C

Table 1. Specific rotation of enantiomeric alcohols **1**, the ^{19}F NMR spectra of their (*S*)-MTPA esters (**5a**), and the enantiomeric purity of alcohol specimens of various origin

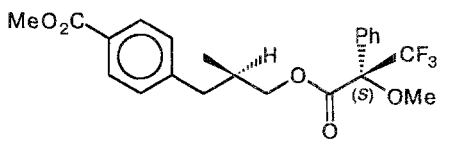
Alcohol	Origin and marking of specimens	Conversion (%)	$[\alpha]_D$ ($CHCl_3$)	δ (rel. peak area) Major peak	Minor peak	*ee* (%)[a]
(*R*)-**1**	PPL-catalyzed hydrolysis of (±)-**2**	50	+2.16°	70.96 (61.1)	70.85 (38.9)	22.2
(*S*)-**1**	Methanolysis of unconverted acetate after the hydrolysis of (±)-**2** with PPL	50	n.d.	70.85 (61.5)	70.96 (38.5)	23.0
(*S*)-**1**	Second hydrolysis of unconverted acetate with PPL, then methanolysis of the recovered acetate (**D**)	44	−3.39°	70.85 (66.5)	70.96 (33.5)	33.0
(*S*)-**1**	Yeast reduction of alkenol **4** (**A**)[b]	—	−9.48°	70.85 (95.0)	70.96 (5.0)	90.0
(*S*)-**1**	Yeast reduction of **4** (**B**)[b]	—	−7.20°	70.85 (87.0)	70.96 (13)	74.0
(*S*)-**1**	Yeast reduction of **4** (**C**)[b]	—	−4.67°	70.85 (70.7)	70.96 (29.3)	41.4

[a] Calculated from the peak areas of (*R*)-**5a** and (*S*)-**5a** in the ^{19}F NMR. [b] Specimen **A** — *Saccharomyces cerevisiae*, strain RCM Y-357; specimen **B** — *S. cerevisiae*, strain RCM Y-407; specimen **C** — *S. cerevisiae*, commercial pressed baker's yeast (GOST 171-81, a product of the Moscow yeast plant).

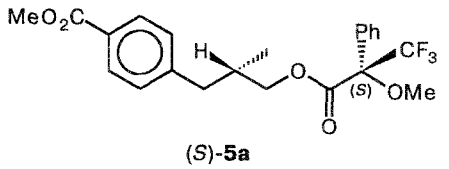
cerevisiae, strains RCM Y-357 and RCM Y-407, or with commercial pressed bakers' yeast fermenting on glucose, alcohol **4** afforded three specimens of levorotatory alcohol (**A**, **B**, and **C**) of various optical purity, depending on the strain. The ^{19}F NMR spectra of their (*S*)-MTPA esters practically coincided with that recorded for the (*S*)-MTPA ester of the levorotatory alcohol produced by treating the fraction of unconverted acetate from the repeated PPL-catalyzed hydrolysis of (±)-**2** with NaOMe in MeOH (Table 1). Hence, this alcohol can be denoted as (*S*)-(−)-**1**.

Finally, the *S* configuration of the levorotatory alcohol was independently confirmed (using specimen **A** as a reference) by the magnitude of the lanthanide induced shift (LIS) observed for the chelated MeO group of the acyl moiety in the ^1H NMR spectra of (*R*)-MTPA and (*S*)-MTPA esters prepared from this reference alcohol. In accordance with earlier observations,[15,16] when the achiral shift reagent, $Eu(fod)_3$, was added to the solutions of these esters in $CDCl_3$ the downfield LIS_{OMe} of the major signal in the spectrum of the (*S*)-MTPA ester, (*S*)-**5a**, was larger than the LIS_{OMe} of the respective signal in the spectrum of the (*R*)-MTPA ester, (*S*)-**5b**. The former was 3.22 ppm while the latter was only 1.84 ppm. The sign and the value of ΔLIS_{OMe} (−1.37 ppm) are similar to those observed for the *S* enantiomers of other primary alcohols possessing a stereogenic carbon atom in the β-position (*cf.* Ref. 16). Therefore, the levorotatory alcohol is actually (*S*)-**1**, and its dextrorotatory counterpart is thus (*R*)-**1**. The difference in the values of LIS_F for the signals of CF_3 in the spectra of (*S*)-**5a** and (*S*)-**5b** supports this conclusion (*cf.* the observations of Oppolzer *et al.*[17]).

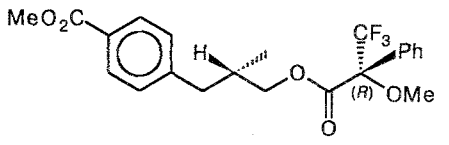
In the PPL-catalyzed hydrolysis of (±)-**2**, there are two points of interest, possibly interrelated, which deserve some comment. First, the reversal of enantioselectivity in favor of the *R* enantiomer, which is not common among 3-carbo-substituted 2-methyl-1-propanols or their *meso*-analogs (see Ref. 5 for exceptions and their explanation). Secondly, the very low enantiomeric ratio, *E* (which characterizes the ratio of the initial rates of conversion for "fast" and "slow" enantiomers), which is inadequate from the preparative point of view. The value of *E* calculated from the Chen—Sih equations[18]



(*R*)-**5a**



(*S*)-**5a**



(*S*)-**5b**

$$E = \ln[(1 - r)(1 - ee_s)]/\ln[1 - r(1 + ee_s)],$$

$$E = \ln[1 - r(1 + ee_p)]/\ln[1 - r(1 - ee_p)],$$

(where the indices s and p relate to the substrate and the product) for the values $ee_p = 0.222$, $ee_s = 0.230$, and $r = ee_s/(ee_s + ee_p) = 0.509$ corresponding to the 50 % conversion of (±)-**2** is only 1.927. This situation is reminiscent of those observed when a cyclohexylmethyl group is substituted for an alkyl group[5] or a benzyl group is substituted for an alkyl[5] or phenyl group[19,20] in

Table 2. Lanthanide induced shifts (LIS) of the signals from the MeO and CF_3 groups in the ^1H and ^{19}F NMR spectra of the (*R*)-MTPA- and (*S*)-MTPA esters obtained from the levorotatory alcohol (*S*)-**1**

MTPA ester	LIS_{OMe}[a]	ΔLIS_{OMe}[b]	LIS_F[a]	ΔLIS_F[b]
(*S*)-**5a**	3.216	−1.373	−1.80	+1.13
(*S*)-**5b**	1.843		−0.67	

[a] The values of LIS (in ppm) relate to the molar ratio (*S*)-**5** : Eu(fod)$_3$ = 4 : 1.
[b] ΔLIS = LIS[(*R*)-MTPA ester] − LIS[(*S*)-MTPA ester] (*cf.* Refs. 15, 16).

2-carbo-substituted 1-propanols, and the reversal of enantioselectivity is accompanied by a substantial or even dramatic decrease in enantioselectivity. In our opinion, these phenomena may be satisfactorily explained by assuming a *conformational substrate model*, which would take into account the ability of PPL to operate in the oil—water interphase[21] and to preferably accomodate the one of the two competing substrates (or conformers) that can more easily adopt the transition state geometry on the active site.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ using a Bruker WM-250 instrument (250 MHz). ^{19}F NMR spectra were taken in $CDCl_3$ on a Bruker AC-200P spectrometer (188.3 MHz) with $CFCl_3$ as the external reference. GC analyses were carried out on an LKhM-80MD gas chromatograph equipped with a flame ionozation detector (stainless steel column, 1.5×0.003 m, 5 % SE-30 on Chromaton N-AW-DMCS, N_2 as the carrier gas, oven isotherm 190 °C). TLC monitoring control was performed in a fixed SiO_2 layer using Silufol plates. Silica gel 40—100 μm (Czech Republic) was used for column chromatography. Optical rotations were measured in $CHCl_3$ on a JASCO DIP 360 polarimeter.

Porcine pancreatic lipase (47.8 U mg^{-1}) was purchased from Olainpharm (Latvia). (*S*)-(−)-MTPA and (*R*)-(+)-MTPA (Fluka AG, Switzerland) were converted to the respective *R* and *S* acyl chlorides by the known procedure,[8] and the latter were immediately used for the derivatization of (+)- and (−) **1**.

Saccharomyces cerevisiae strains RCM Y-357 and RCM Y-407 were kindly provided by the Russian Collection of Microorganisms. Commercial fresh pressed baker's yeast (GOST 171-81, produced by the Moscow yeast plant) were purchased from Mosagroprom, Moscow, and checked for injured cells and microbial infection before use. All new compounds gave satisfactory data upon elemental analysis.

3-(4-Methoxycarbonyl)phenyl-2-methyl-2-propen-1-ol (4). Aldehyde **3** (m.p. 74—75 °C, from MeOH) was obtained according to Ref. 3. A saturated solution of **3** (2 g, 9.8 mmol) in MeOH was added at −10 °C to a stirred suspension of $NaBH_4$ (0.19 g, 5 mmol) in MeOH (10 mL). The reaction mass was stirred at −5 tp −10 °C for 4 h and then left overnight. The solvent was removed under reduced pressure, and the residue was diluted with water (5 mL) and extracted with Et_2O (3×15 mL). The extract was dried with Na_2SO_4 and evaporated to afford alcohol **4** as a slightly yellowish oil. Yield: 2.05 g (quantitative). ^1H NMR (δ, *J*/Hz): 1.85 (s, 3 H, Me—C=C); 3.52 (d, 2 H, CH_2OH, J = 1.8); 4.20 (s, 3 H, CO_2Me); 6.55 (s, 1 H, HC=C); 7.2—8.1 (dd, 4 H, A_2B_2 system, J_{AB} = 8). R_t = 7.03 min.

3-(4-Methoxycarbonyl)phenyl-2-methyl-1-propanol, (±)-1. Alcohol **4** (2.06 g, 10 mmol) was dissolved in MeOH (10 mL) and hydrogenated over a 5 % Pt/C catalyst at room temperature and atmospheric pressure. After consumption of 10 mmol of H_2 (48 h) the catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in Et_2O and purified by filtration through a column of silica gel. Pure (±)-**1** was thus isolated as a colorless oil. Yield: 1.79 g (86 %). ^1H NMR (δ, *J*/Hz): 0.91 (d, 3 H, MeCH, J = 6.5); 1.95 (m, 1 H, MeCH); 2.4 and 2.75 (dd + dd, 2 H, the AB part of ABC system, $ArCH_2$, J_{AB} = 14, $J' \approx$ 6.5); 3.50 (d, 2 H, CH_2OH, J = 6.5); 3.80 (br.s, 1 H, OH); 3.95 (s, 3 H, CO_2Me); 7.25 and 7.85 (dd + dd, 4 H, the A_2B_2 system, J_{AB} = 8). R_t = 6.0 min.

3-(4-Methoxycarbonyl)phenyl-2-methylprop-1-yl acetate, (±)-2. A mixture of (±)-**1** (1.7 g, 8.2 mmol), acetic anhydride (1.25 g, 12.3 mmol), and pyridine (0.62 mL, 8 mmol) was stirred at 20—22 °C for 4.5 h. The reaction mass was diluted with water and extracted with Et_2O (20 mL). The extract was washed successively with 1 *M* HCl, saturated aqueous $NaHCO_3$, and water, then dried with Na_2SO_4 and evaporated to leave the pure acetate, (±)-**2**, as a colorless oil. Yield: 1.8 g (89 %). ^1H NMR (δ, *J*/Hz): 0.90 (d, 3 H, MeCH, J = 6.5); 2.03 (s, 3 H, MeCO); 2.15 (m, 1 H, MeCH); 2.25 and 2.85 (dd + dd, 2 H, the AB part of the ABC system, $ArCH_2$); 3.97 (s, 3 H, CO_2Me); 4.05 (br.s, 2 H, CH_2OAc, J = 6.5); 7.2 and 7.9 (dd + dd, 4 H, the A_2B_2 system, J_{AB} = 8). R_t = 8.5 min.

Enzymatic hydrolysis of the acetates. General procedure. Sterilized 0.1 *M* phosphate buffer (pH 6.5) and the oily racemic acetate, (±)-**2**, taken in a proportion of ≈ 58 : 42 (w/w), were placed into a round-bottom flask equipped with a magnetic stirring bar. The oil was dispersed in the buffer by vigorous stirring, and dry powdered PPL was added to the emulsion. The flask was stoppered, and the stirring continued at 20—22 °C to attain 43—50 % conversion (GC and TLC

Table 3. Enzymatic hydrolysis of acetates in the presence of PPL (0.1 *M* phosphate buffer, pH 6.5, 20—22 °C)

Entry	Substrate, *m*/g	PPL, *m*/g	Time /h	Conversion (%)	Isolated alcohol			Residual acetate		
					$[\alpha]_D$	Yield (%)	*ee* (%)	$[\alpha]_D$	Yield (%)	*ee* (%)
1	(±)-**2** (0.25)	0.125	3.5	50±2	+2.16°	67	22.2	+3.28°	80	23
2	(+)-**2** (1.80)	0.180	24	43±2	+2.72°	70	27.0	n.d.	93	n.d.
3	(*S*)-**2**[a] (1.00)	0.100	24	44±2	n.d.	87	n.d.	+3.46°	92	33[b]

[a] Residual acetate recovered from the scale-up experiment (entry *2*). [b] Determined from the spectrum of the MTPA ester, (*S*)-**5a**, prepared from specimen **D** of the alcohol (*S*)-**1D** (*cf.* Table 1).

Table 4. Biohydrogenation of alkenol **4** with various strains of *Saccharomyces cerevisiae*

Entry	Strain	Substrate, *m*/g	Initial biomass, *m*/g	Characteristics of the process[a]			
				Conversion (%)	Specimen (*S*)-**1**	Yield (%)	*ee* (%)
1	RCM Y-357	1.00	33.3	34[b]	**A**	20	90
2	RCM Y-407	1.04	33.3	33[c]	**B**	15	74
3	Commercial B.Y. (GOST 171-81)	1.00	33.3	42[d]	**C**	22	41.4

[a] Fermentation temperature: 28 °C (entries *1* and *2*), or 35 °C (entry *3*). The characteristics (conversion, yield, *ee*) correspond to the maximum accumulation of (*S*)-**1** in the culture broth. [b] After 48 h of fermentation. [c] No change between 48 and 72 h of fermentation. [d] After 72 h.

monitoring). Then the reaction mass was neutralized with saturated aqueous $NaHCO_3$ and filtered through a pad of Celite (6—10 g) to remove the bulk of the PPL. The solid cake was washed with Et_2O, and the aqueous phase of the moist ethereal eluate was extracted with Et_2O (5×10 mL). The combined organic layer was washed with a little water and brine, dried with Na_2SO_4, and evaporated. The oily residue was chromatographed on a column of SiO_2 using a hexane—Et_2O gradient (0→100 % Et_2O). Elution with hexane—Et_2O 50 : 50 (v/v) gave the unreacted acetate; more polar eluates contained the alcohol fraction enriched in (*R*)-(+)-**1** (*ee* 22—27 %).

In the same way, the hydrolysis of the recovered acetate fraction afforded a specimen of the acetate enriched in (*S*)-(+)-**2** (*ee* ≈ 33 %). The exact conditions of the experiments and the characteristics of the products thus obtained are presented in Table 3.

(*R*)-(+)-3-(4-Methoxycarbonyl)phenyl-2-methyl-1-propanol, (*R*)-1. The crude residue obtained after the 50 % conversion of (±)-**2** (Table 3, entry *1*) was chromatographed on a column of SiO_2 (6 g) to afford a fraction of unconverted acetate, mainly (*S*)-(+)-**2** (100 mg, 80 % recovery), and an alcohol fraction as a colorless oil with $[\alpha]_D^{22}$ +2.16° (*c* 2.5), enriched in (*R*)-(+)-**1**. Yield: 70 mg (67 %). Similarly, the crude residue left from the scaled-up hydrolysis at a higher substrate-to-enzyme ratio and 43 % conversion (see Table 3, entry *2*) was fractionated by column chromatography on 46 g of SiO_2 to yield 1.0 g of unconverted acetate (93 % recovery) and 462 mg of chromatographically pure alcohol, (*R*)-(+)-**1** with $[\alpha]_D^{22}$ +2.72° (*c* 2.4). Yield: 70 %.

The reduction of alcohol 4 with bakers' yeast. The cultures of *S. cerevisiae* (strains RCM Y-357 and RCM Y-407) were sustained on brewers' wort agar. The active yeast biomass was grown on brewers' wort (7 °Blg) for 48 h at 28 °C in a shaken culture (120 r.p.m.). The biomass was separated by centrifugation and transferred to the medium of the following composition (g L^{-1}): maize corn extract — 5, D-glucose — 20, yeast extract — 3, $NaNO_3$, K_2HPO_4 — 1, $MgSO_4$ — 0.5, KCl — 0.5, $FeSO_4$ — 0.01, sterilized tap water (pH 6.0); 2 g of the biomass (fresh weight) per 100 mL of culture medium was taken for each flask. The substrate (alcohol **4**) was introduced to the culture as a 3 % solution in EtOH; care was taken that the content of EtOH in the culture be no more than 2 per cent. Incubations were carried out at 28 °C on a shaking machine (120 r.p.m.). After 24 and 48 h of fermentation aliquotes of the culture broth were taken for analysis, and additional portions of the fresh biomass (aged no longer than 24 h, 10 g L^{-1}) and glucose (10 g L^{-1}) were added to the culture; if necessary, yet another addition was done after 72 h of fermentation. Incubations were continued until the maximum accumulation of the target alkanol in the culture broth was attained (GC and TLC control). Then the cultures were harvested, filtered through a pad of gauze, and the filtrate (a fine cell suspension) was repeatedly extracted with Et_2O in a two-neck round-bottom flask provided with a mechanical stirrer.

Each time, the extracts were carefully decanted from the aqueous cell suspension, and the combined organic layer (from 4—5 extractions, *ca.* one third of the volume of the culture filtrate) was evaporated. The resulting wet oily residue was treated with 10 % aqueous NaOH and re-extracted in Et_2O. The extract was washed with brine and water, dried with Na_2SO_4, and evaporated to leave an oily residue that contained the target alkanol, (*S*)-**1**, and unconverted substrate **4**. In order to remove this contaminant the residue was dissolved in $CHCl_3$ and stirred for 24 h (~20 °C) with *ca.* three equivalents of "alkaline" active manganese dioxide prepared according to Ref. 22. The resulting mixture of (*S*)-**1** with aldehyde **3** was chromatographed on a column of SiO_2 (30 parts of SiO_2 per 1 part of the adsorbate). Gradient elution with hexane—Et_2O (from 0 to 50 % Et_2O, v/v) afforded the target alcohol (*S*)-**1**.

The biohydrogenation of alkenol **4** with commercial fresh pressed baker's yeast and subsequent work-up were performed similarly but without growing the active biomass; the temperature was kept at 35 °C. The results obtained with various strains of *S. cerevisiae* are presented in Table 4. In all cases prolongation of the process beyond the period indicated in Table 4 brought about the randomization of the target alcohol.

(*S*)-(−)-3-(4-Methoxycarbonyl)phenyl-2-methyl-1-propanol, (*S*)-1. ***A.*** Using the yeast reduction of alkenol **4**, the following specimens of (*S*)-**1** were obtained: **A** — yield 202 mg (20 %), $[\alpha]_D^{20}$ −9.48° (*c* 2.73); **B** — yield 158 mg (15 %), $[\alpha]_D^{20}$ −7.20° (*c* 2.25); **C** — yield 222 mg (22 %), $[\alpha]_D^{21}$ −4.67° (*c* 2.50). The origin of specimens and the amounts of substrate used are indicated in Table 4.

B. The fraction of residual acetate (520 mg, 2.08 mmol) obtained as shown in Table 3 (entry *3*) was treated at 20—22 °C with a methanolic solution of NaOMe prepared from 5 mg of sodium (0.21 mmol) and 5 mL of MeOH. After 30 min, the reaction was quenched with glacial AcOH (1.5 mL), and the solvent was evaporated under reduced pressure. The oily residue was diluted with water (3 mL) and extracted with Et_2O (4×3 mL). The extract was washed with saturated aqueous $NaHCO_3$ and water, dried with Na_2SO_4, and evaporated to give yet another specimen of (*S*)-**1** (specimen **D**), yield 377 mg (87 %), $[\alpha]_D^{23}$ −3.39° (*c* 2.30).

The values of *ee* for various specimens of (*S*)-**1**, given in Tables 1, 3, and 4, were determined from the ^{19}F NMR spectra of the respective specimens of the (*S*)-MTPA esters, (*S*)-**5a**.

(*S*)-(+)-Acetate, (*S*)-2. Specimen **A** of alcohol (*S*)-**1** was acetylated in the same manner as described for the preparation of (±)-**2**. The ^{1}H NMR spectra and the R_f values of the resulting (*S*)-**2** practically coincided that of (±)-**2**. The acetate obtained from (*S*)-(−)-**1** was dextrorotatory: $[\alpha]_D^{21}$ +7.87° (*c* 2.08).

MTPA esters of alcohols (*R*)-(+)-1 and (*S*)-(−)-1. General procedure. A solution of the (*R*)- or (*S*)-chloroanhydride prepared from (*S*)-(−)- or (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (0.15 mmol), respectively, in dry pyridine (0.15 mL) was added to a solution of (*R*)-**1** or (*S*)-**1** (20 mg, 0.096 mmol) in dry CCl_4 (30 μL). After 10 min of exposure, the mixture was treated with a solution of 2-dimethylaminoethylamine (Fluka AG, 0.096 mmol) in 15 mL of dry CCl_4 and, 10 min later, with 1 *M* HCl (2 mL). The reaction product was extracted with Et_2O (3×1 mL); the extract was successively washed with 1 *M* HCl, saturated aqueous $NaHCO_3$, and water, dried with Na_2SO_4, and evaporated to give a chromatographically pure specimen of the MTPA ester which was characterized by ^{1}H NMR) spectroscopy (see below).

(*S*)-MTPA ester of alcohol (*R*)-(+)-1, (*R*)-5a. ^{1}H NMR (δ, *J*/Hz): 0.93 d > 0.95 d (3 H, MeCH, *J* = 6.6); 2.18 (m, 1 H, CHMe); 2.47 and 2.72 (dd + dd, 2 H, the AB part of the ABC system, J_{AB} = 15, *J'* = 6.5); 3.58 s > 3.56 s (3 H, OMe in the acyl moiety); 3.92 (s, 3 H, CO_2Me); 4.14 d > 4.16 d (2 H, CH_2OCOR*); 7.18 and 7.96 (dd + dd, 4 H, the A_2B_2 system, J_{AB} = 8.5); 7.42 (m, 5 H, Ph).

(*S*)-MTPA ester of alcohol (*S*)-(−)-1, (*S*)-5a, prepared from specimen **A** (see Table 4, *ee* 90 %). ^{1}H NMR (δ, *J*/Hz): 0.945 (d, 3 H, MeCH, *J* = 6.6); 2.18 (m, 1 H, CHMe); 2.46 and 2.70 (2 H, the AB part of the ABC system, J_{AB} = 15, *J'* = 6.5); 3.56 (s, 3 H, OMe in the acyl moiety); 3.90 (s, 3 H, CO_2Me); 4.16 (d, 2 H, CH_2OCOR*, *J* = 6.5); 7.15 and 7.96 (dd + dd, 4 H, the A_2B_2 system, J_{AB} = 8.5); 7.43 (m, 5 H, Ph).

(*R*)-MTPA ester of alcohol (*S*)-(−)-1, (*S*)-5b, prepared from specimen **A** (see Table 4, *ee* 90 %). In the absence of Eu(fod)$_3$ the ^{1}H NMR of (*S*)-**5b** was qualitatively identical with that of (*S*)-**5a** (see also Table 2).

The authors express their gratitude to the Russian Foundation for Basic Research for financial support (Grant No. 93-03-5893).

References

1. K. Nakamoto, T. Suzuki, S. Abe, K. Hayashi, and A. Kajiwara (Eisai Co. Ltd), Eur. Pat. Appl. EP 194693; *Chem. Abstrs.*, 1989, **111**, 57300.
2. G. V. Kryshtal, G. M. Zhdankina, and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 2126 [*Russ. Chem. Bull.*, 1993, **42**, 2039 (Engl. Transl.)].
3. G. V. Kryshtal, G. M. Zhdankina, and E. P. Serebryakov, *Zh. Org. Khim.*, 1994, **30**, 732 [*Russ. J. Org. Chem.*, 1994, **30**, No. 5 (Engl. Transl.)].
4. J. Ehrler, D. Seebach, *Liebigs Ann. Chem.*, 1990, 379.
5. G. Guanti, L. Banfi, and E. Narisano, *J. Org. Chem.*, 1992, **57**, 1540.
6. D. Bianchi and P. Cesti, *J. Org. Chem.*, 1990, **55**, 5657.
7. R. Bhide, R. Mortezaei, A. Schlimati, and C. J. Sih, *Tetrahedron Lett.*, 1990, **31**, 4827.
8. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
9. P. Gramatica, P. Manitto, and L. Poli, *J. Org. Chem.*, 1985, **50**, 4625.
10. H.-E. Högberg, E. Hedenström, and J. Fägerhäg, *J. Org. Chem.*, 1992, **57**, 2052.
11. C. Fuganti and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, 1979, 995.
12. P. Gramatica, P. Manitto, D. Omonti, and G. Speranza, *Tetrahedron*, 1988, **44**, 1299.
13. C. Fuganti and P. Grasselli, *Chem. and Ind.*, London, 1977, 983.
14. C. Fuganti, P. Grasselli, S. Servi, and H.-E. Högberg, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3061.
15. F. Yasuhara and S. Yamaguchi, *Tetrahedron Lett.*, 1977, 4085.
16. Y. Sugimoto, T. Tsuyuki, Y. Moriyama, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3723.
17. W. Oppolzer, M. Kurth, D. Reichlin, and F. Moffatt, *Tetrahedron Lett.*, 1981, **22**, 2545.
18. C.-S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294.
19. G. Guanti, E. Narisano, T. Podgorski, S. Thea, and A. Williams, *Tetrahedron*, 1990, **46**, 7081.
20. G. M. Ramos Tombo, H.-P. Schär, X. Fernandez-i-Busquets, and O. Ghisalba, *Tetraherdon Lett.*, 1986, **27**, 5707.
21. H. Brockerhoff and R. G. Jensen, in *Lipolytic Enzymes*, Academic Press, New York, 1974, 34.
22. J. Attenburrow, A. Cameron, J. H. Chapman, R. M. Evans, B. A. Hens, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

Received November 21, 1994