Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 10, pp. 2983-2996, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00389-8

Selective Synthesis of 1-, and 3-Carbomethoxy 2-Tetralol Stereoisomers by Microbial Reduction of the Corresponding Tetralones

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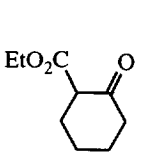
Abstract: The microbial reduction of β-ketoesters derived from 2-tetralone has been shown to produce good yields of 2-hydroxy-1-carboxy- or 3-hydroxy-2-carboxyesters. Baker's yeast invariably affords a high enantiomeric purity *cis*-hydroxyester, while fungi strains may produce, sometimes exclusively, *cis*- or *trans*- complementary stereochemistries. From a general survey of the baker's yeast reduction of cyclic β-ketoesters, a working model for predicting enantio- and diastereoselectivities of the reduction is proposed and discussed. Copyright © 1996 Elsevier Science Ltd

Asymmetric synthesis using enzymes or microorganisms is now a methodology of increasing interest for organic chemists. Among the most promising methods recently developed, the deracemizing microbial reduction of α-substituted β-ketoesters [1-4] gives access in high yields to one of the corresponding α-substituted β-hydroxyesters stereoisomers, and may compete with the analogous catalytic asymmetric hydrogenation methods ("kinetic dynamic resolution") [5-12]. Baker's yeast, a readily available microorganism, has been mostly used for such reductions [13]. The first example found in the literature described the reduction of ethyl cyclohexanone-2 carboxylate **1** into ethyl (1*R*,2*S*)-2-hydroxycyclohexane carboxylate [1] in good yield (70-80%) and high enantiomeric excess. This example demonstrated the ability of baker's yeast to reduce such substrates with high enantioselectivity (both towards substrate and product) combined with the fast equilibration of substrate enantiomers. A number of similar reductions of cyclic [14-25] and non cyclic [2,3,26-38] variously substituted β-ketoesters have been since described and used for synthetic purposes, and a simple model for explaining the diastereoselectivity features of baker's yeast-mediated reductions has been proposed [39]. However, yeast was not always an efficient catalyst and could not afford any possible isomer. Several more or less successful attempts to modify the diastereo- and/or enantioselectivity features of microbial reductions have been reported: increase of the size of the alkyl ester group [30,40], aging of biocatalyst [35,41], heat treatment [42,43], addition of dehydrogenase inhibitors [42-44], use in organic solvents [45,46], etc. These procedures are mainly based on modifications of the enzymatic equipment or activities of the yeast cell [47-52], hypothetically favoring the dehydrogenase activity(ies) involved in the desired stereoselective biotransformation. We have previously shown[4] that the use of other microorganisms (mainly other yeast or fungi strains) under similar reduction conditions could provide efficiently different hydroxyester isomers. For instance, *Rhizopus arrhizus* was able to reduce ethyl cyclohexanone-2-carboxylate **1** to enantiomerically pure (1*S*,2*S*)-hydroxyester as the major product, while baker's yeast mainly afforded the (1*R*,2*S*) isomer.

Recently, we have investigated [53] the reduction of 2-carboxyethyl-1-tetralone **2** by various microorganisms and succeeded in preparing in good yield and high enantiomeric excess both enantiomers of the corresponding *cis*-hydroxyester: the (1*R*,2*R*)-hydroxyester was obtained by using another yeast strain (*Saccharomyces montanus*), and the (1*S*,2*S*) isomer by using a fungal strain (*Mucor racemosus*). In order to understand better the structural parameters which determine the stereospecificity of these reductions, and eventually build a model for this reaction, we have similarly investigated the reduction of the β-tetralone-derived ketoesters **3** and **4**. Previous attempts to use baker's yeast in such reductions have been marginally successful [18]. Nevertheless, the corresponding enantiomerically pure hydroxyesters may constitute versatile homochiral synthons for the

preparation of useful chiral auxiliaries such as aminoalcohols or oxazolidinones, by analogy with the already used *cis*-amino indanol derivatives [54-57].



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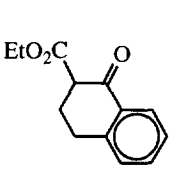

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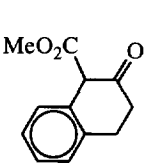

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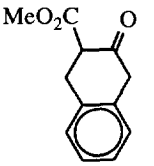

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RESULTS

Substrates **3** and **4** were prepared from β-tetralone as previously described in the literature. Carboxylation in position -1 was obtained by reaction with dimethylcarbonate in the presence of sodium hydride [58]. The reaction of β-tetralone with magnesium methyl carbonate afforded 2-tetralone-3-carboxylic acid which was esterified with diazomethane [59]. The corresponding racemic diastereomeric hydroxyesters were obtained by reduction with sodium borohydride, analytically separated by GC, and their relative configurations were assigned by ^{1}H-NMR on purified products.

Microbial reductions were performed in the culture media. After full growth of the microorganisms, ketoesters **3** or **4** were added as a solution (10% w/v) in an ethanol-Tween 80 (8:2) mixture to obtain a 1 g.L^{-1} final concentration. The reaction rate and the *cis/trans* ratio of hydroxyesters produced by reduction were determined by GC of crude incubation extracts. Enantiomeric excesses were measured after derivatization to (*S*)-O-acetyllactyl esters and analysis by GC in conditions where the derivatized racemic diastereomers mixture exhibited four peaks.

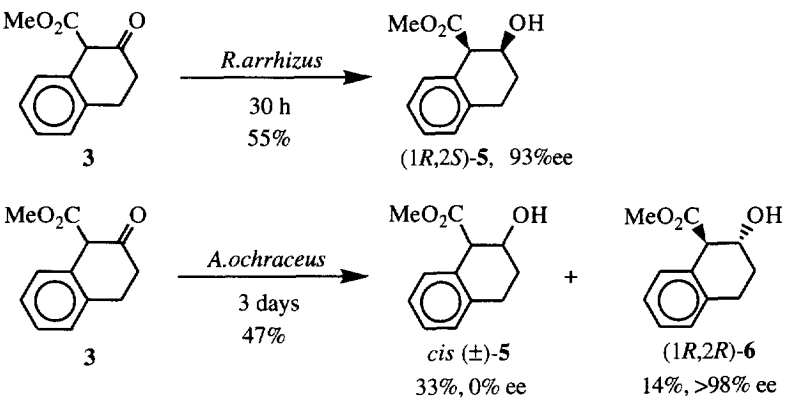
Reduction of 1-carbomethoxy-2-tetralone **3**. All yeast (6) and fungal strains (19) tested were able to reduce the ketoester **3**. Most significant results are summarised in Table 1. The reduction was faster with some fungi, for example *M. racemosus* (7 h) and *S. exile* (5 h), or slower with others (1-3 days). However, the reaction time was generally longer (but the reduction was complete) with yeasts (*S. montanus* or *S. cerevisiae*). The (1*R*) enantiomer of the substrate was always preferentially reduced. The stereochemistry of the reduction was *S* and the product thus invariably exhibited a major *cis* (1*R*,2*S*) configuration **5** except for the *cis* isomer obtained by reduction with *A. ochraceus*, which was racemic. Only two strains, *S. montanus* and *A. ochraceus* afforded significant amounts of the *trans* isomer (12 and 35% respectively). In both cases the stereochemistry of the reduction was exclusively *R* and the configuration of the *trans* reduction product was 1*R*,2*R*.

Table 1. Stereochemistry and Enantiomeric Excesses of the Microbial Reduction Products of **3**

Microorganisms	Reduction time (hours)	Hydroxyesters						
				cis			*trans*	
		(%)[a]	%	abs.conf.	(ee %)	%	abs.conf.	(ee %)
Saccharomyces cerevisiae	24	74	99	(1*R*,2*S*)	(91)	1	-	-
Saccharomyces montanus CBS 6772	168	87	88	(1*R*,2*S*)	(89)	12	(1*R*,2*R*)	(>98)
Rhizopus arrhizus ATCC 11145	24	100	96	(1*R*,2*S*)	(94)	4	-	-
Mucor racemosus	7	97	96	(1*R*,2*S*)	(94)	4	-	-
Sporotrichum exile QM 1250	5	96	99	(1*R*,2*S*)	(87)	1	-	-
Aspergillus ochraceus ATCC 1009	72	95	65	-	(0)	35	(1*R*,2*R*)	(>98)
Rhodotorula glutinis NRRL Y1091	96	95	99	(1*R*,2*S*)	(93)	1	-	-

[a] determined by GC of the crude incubation extract.

The methyl (1*R*,2*S*)-2-hydroxy-1,2,3,4-tetrahydronaphthalene 1-carboxylate **5** was obtained on a preparative scale by using *R. arrhizus* ATCC 11145 for the reduction of the ketoester **3** (yield 55% after chromatography, 93% ee) (Scheme 1). The *trans* methyl (1*R*,2*R*)-2-hydroxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate **6** was prepared by reduction of **3** with *A. ochraceus* ATCC 1009, followed by chromatogaphic separation from the *cis* isomer (14% isolated yield, >98% ee) (Scheme 1).



Scheme 1

Reduction of 3-carbomethoxy-2-tetralone ***4***.

Some microorganisms active in the reduction of ketoesters **1**, **2** and **3** (Table 2) were preliminarily tested. Reduction of the ketoester **4** was fast, except with *R. arrhizus*. A mixture of diastereomers was sometimes obtained. However, three hydroxyester stereoisomers were found to be formed as major reduction products, *cis* (2*S*,3*R*) with yeast strains (baker's yeast and *S. montanus*), *cis* (2*R*,3*S*) with *A. ochraceus*, and *trans* (2*S*,3*S*) with *M. racemosus* or *R. glutinis*.

Table 2. Stereochemistry and Enantiomeric Excesses of the Microbial Reduction Products of **4**

Microorganisms	Reduction time (hours)	Hydroxyesters						
			cis			*trans*		
		(%)[a]	%	abs.conf.	(ee %)	%	abs.conf.	(ee %)
Saccharomyces cerevisiae	24	67	99	(2*S*,3*R*)	(72)	1	-	-
Saccharomyces montanus CBS 6772	24	75	97	(2*S*,3*R*)	(83)	3	-	-
Rhizopus arrhizus ATCC 11145	96	50	31	(2*S*,3*R*)	(27)	69	(2*S*,3*S*)	(89)
Mucor racemosus	30	89	10	(2*S*,3*R*)	(50)	90	(2*S*,3*S*)	(93)
Sporotrichum exile QM 1250	24	92	24	(2*S*,3*R*)	(25)	76	(2*S*,3*S*)	(94)
Aspergillus ochraceus ATCC 1009	48	72	95	(2*R*,3*S*)	(89)	5	-	-
Rhodotorula glutinis NRRL Y1091	24	80	5	-	-	95	(2*S*,3*S*)	(95)

[a] determined by GC of the crude incubation extract.

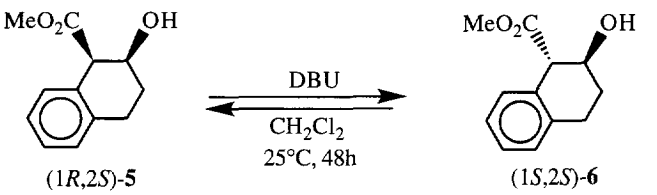
S. montanus and *A. ochraceus* have been used on a preparative scale (Table 3) to prepare in good yields and moderate enantiomeric excesses the *cis* methyl (2*S*,3*R*)- and (2*R*,3*S*)-3-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylates **7**, respectively. The *trans* (2*S*,3*S*)-hydroxyester was similarly produced in high yield and high enantiomeric purity by using *M. racemosus*.

Table 3. Preparative Microbial Reductions of **4** to Hydroxyesters **7** or **8**

Microorganims	Reduction time (h)	Yield (%)	Absolute configuration	ee (%)	$[\alpha]_D$ (c 1, $CHCl_3$)
S. montanus CBS 6772	10	53	2*S*,3*R*	77	– 18
A. ochraceus ATCC 1009	20	51	2*R*,3*S*	85	+ 21
M. racemosus	24	76	2*S*,3*S*	94	+ 135

Determination of absolute configurations.

The (1*R*,2*S*) configuration of the *cis* hydroxyester **5** obtained by reduction of **3** with *R. arrhizus* was determined by comparison of its specific rotation $[\alpha]^{20}_D$– 40 (c 1, $CHCl_3$), with the literature value given for the corresponding ethyl ester, $[\alpha]^{20}_D$– 56 (c 1, $CHCl_3$) [60]. The (1*S*,2*S*)*trans* isomer **6** was obtained by epimerization of the C-1 carbon atom upon mild treatment with DBU in dichloromethane (Scheme 2). The GC analysis of the equilibrium mixture, after derivatization with (*S*)-O-acetyllactyl chloride, allowed the separate assignment of the retention times of enantiomeric pairs for each diastereomeric ester. The minor *trans* reduction product of **3** obtained with *A. ochraceus* was found to be enantiomeric of the (1*S*,2*S*) epimerized product formed from (1*R*,2*S*)-**5**, and thus was assigned a (1*R*,2*R*)-configuration .



(1*R*,2*S*)-**5** (1*S*,2*S*)-**6**

Scheme 2

The absolute configuration of the *trans* hydroxyester **7**, resulting from the reduction of **4** with *M. racemosus*, was fully assigned as (2*S*,3*S*) by an X-ray crystallographic analysis [61] of its camphanate ester **9**, prepared from (–)-(1*S*,4*R*)-camphanic acid chloride (figure 1).

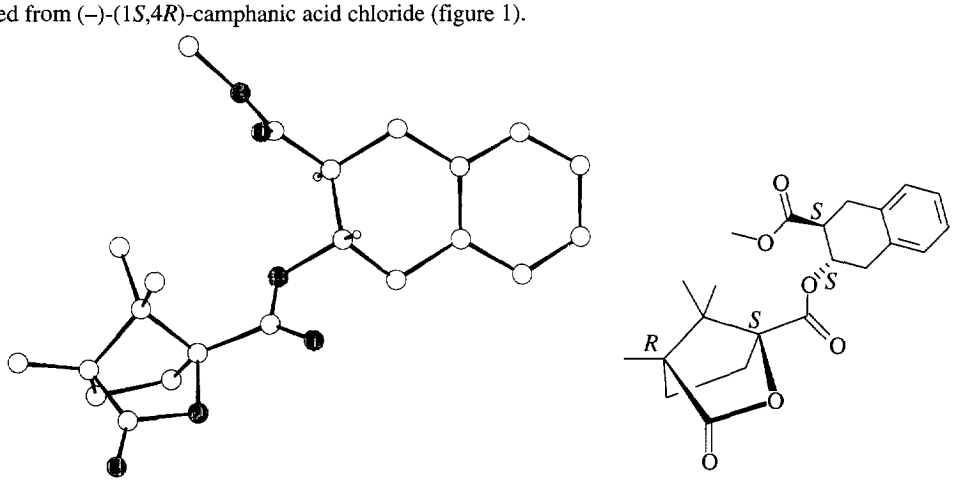
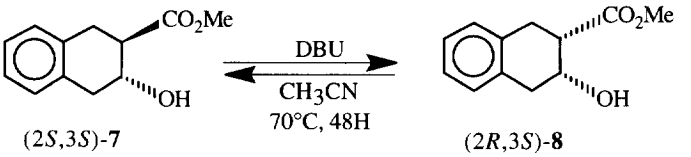


Fig. 1. X-ray structure and stereochemistry of the camphanate ester **9**

The acidic α-hydrogen of the methyl 3-hydroxy-1,2,3,4-tetrahydronaphtalene-2-carboxylate **7**, which is not in a benzylic position, was more difficult to abstract, and partial epimerization was accomplished by heating with DBU at 70°C in acetonitrile (Scheme 3). Under such conditions, the *trans* (2*S*,3*S*)-hydroxyester **7** (obtained

by reduction with *M. racemosus*) equilibrated with the *cis* (2*R*,3*S*)-hydroxyester **8**. After derivatization to its (*S*)-O-acetyllactyl ester, the epimerized *cis*-hydroxyester showed a GC-retention time identical to that of the hydroxyester obtained by reduction with *A. ochraceus* , which was thus assigned a (2*R*,3*S*) configuration.

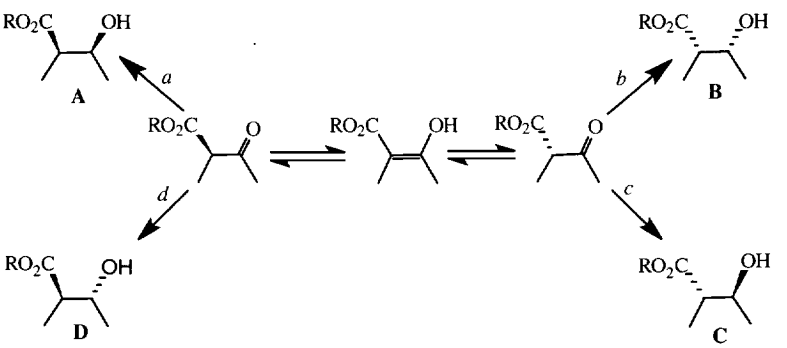


(2*S*,3*S*)-**7** (2*R*,3*S*)-**8**

Scheme 3

DISCUSSION

The enzymic reduction of α-substituted β-ketoesters can follow any of the *a,b,c* or *d* pathways illustrated in Scheme 4, depending on the dual stereospecificity of the reduction enzyme(s) involved: one results from the ability of enzyme(s) to discriminate between the enantiomeric faces of the carbonyl group in the reduction reaction (*stereogenic specificity*); while the second is the ability to discriminate between both enantiomers of the substrate, one of them being transformed faster, or exclusively, to the product (*enantiomeric specificity*). With the use of stereochemically unstable substrates, such as α-substituted-β-ketoesters, this may lead to the major or exclusive production of a single stereoisomer ("dynamic kinetic resolution" [5]).

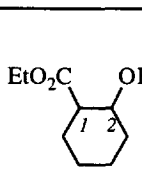
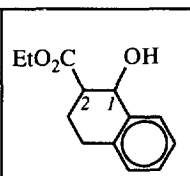
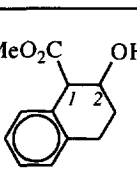
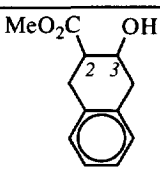


Scheme 4

It was thus interesting to compare the stereospecificity of the reduction of the different substrates **1**, **2**, **3** and **4** by some microorganisms, as summarised in Table 4. For this purpose the (*R/S*) nomenclature was not well-adapted and the results are presented by type products **A**, **B**, **C** or **D**, as resulting from the corresponding pathways illustrated in Scheme 4. Quite evidently both stereospecific abilities have to be dependent on the size and spatial disposition of the substituents, particularly the aromatic ring of the carboxytetralone substrate, and also on the particular strain (enzyme) employed for the reduction.

The first observation is that baker's yeast always affords the same type **A** *cis*-product, as incidentally noted by Seebach *et al.* [18]. The other *Saccharomyces* strain (*S. montanus*) exhibits an identical stereospecificity. Another observation is the disparity observed in the reduction types produced by other microorganisms. Sometimes, a mixture of stereoisomers is obtained with some substrates (type **A** products being most generally observed), probably as the result of the activity of several enzymes. However it is interesting to note the results obtained with *M. racemosus,* which gives three (**A**, **B** and **C**) of the four possible stereoisomeric structures in the reduction of **1** and **3**, **2** and **4** respectively.

Table 4. Stereochemistry of the Reduction Products of Cyclic β-Ketoesters **1-4**. Abbreviated denominations **A** to **D**, see Scheme 4. Percentages indicate relative amounts of hydroxyesters (only amounts above 5-10% have been considered).

				
Baker's yeast	(1*R*,2*S*) **A**	(1*R*,2*R*) **A**	(1*R*,2*S*) **A**	(2*R*,3*S*) **A**
S. montanus	(1*R*,2*S*) **A**	(1*R*,2*R*) **A**	(1*R*,2*S*) **A**	(2*R*,3*S*) **A**
M. racemosus	(1*R*,2*S*) **A**	(1*S*,2*S*) **B**	(1*R*,2*S*) **A**	(2*S*,3*S*) **C**
R. arrhizus	(1*S*,2*S*) **C** (70%) (1*R*,2*S*) **A** (30%)	(1*S*,2*S*) **B**	(1*R*,2*S*) **A**	(2*S*,3*S*) **C** (70%) (2*R*,3*S*) **A** (20%) (2*S*,3*R*) **B** (10%)
A. ochraceus	(1*R*,2*S*) **A** (75%) (1*S*,2*R*) **B** (25%)	no reduction	(1*R*,2*S*) **A** (30%) (1*S*,2*R*) **B** (30%) (1*R*,2*R*) **D** (40%)	(2*S*,3*R*) **B**
R. glutinis	(1*R*,2*R*) **A**	(1*R*,2*R*) **A** (60%) (1*R* ,2*S*) **C** (40%)	(1*R*,2*S*) **A**	(2*S*,3*S*) **C**

Concerning the stereogenic specificity, the reduction of α-substituted-β-ketoesters performed by baker's yeast generally follows the Prelog's rule [62], the larger substituent being considered as the disubstituted α-carbon, and the smaller substituent corresponding to the alkyl chain. In such a model, the hydride is delivered from the *Re* face of the keto group, producing *S*-alcohol isomers (excepted for the presence of heteroatoms interferring in the precedence order). An additional model has been proposed by Van Middlesworth and Sih [39], to predict the preferred stereochemistry of the α-substituted carbon of aliphatic α-subtituted β-hydroxyesters resulting from the dynamic kinetic resolution by baker's yeast (Figure 2). The size and hydrophobicity of the α-substituent and of the ester group determine which group can be accepted in the smaller pocket of the model, the larger α-ligand residing in the same plane as the carbonyl group, and the hydrogen localization being restricted to the upper position. In the aliphatic α-substituted β-ketoester series, the incoming of the hydride ion from the upper face (*Re* face) of the ketone, opposite to the smaller site, induces the formation of a major *syn* reduction product from ketoesters bearing a small α-substituent, and the formation of a major *anti* product from ketoesters bearing a large α-substituent.

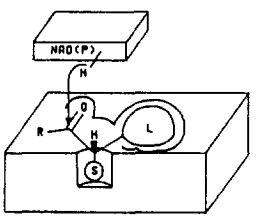


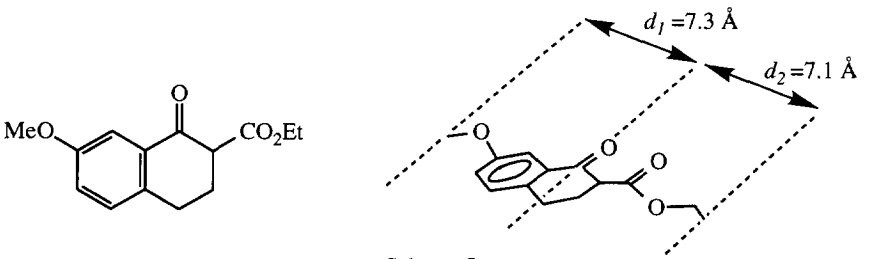
Fig. 2: Model of enzyme active site leading to diastereoselective reduction by Baker's yeast (adapted from [39])

It is difficult to fit into this model even the simpler cyclic α-substituted β-ketoesters, because only one of the predicted arrangements of the α-carbon substituents is possible: the formation of a *cis* product, which is

indeed that mainly or exclusively observed in all reductions of these cyclic ketoesters by baker's yeast, requires the assumption of a unique and unfavorable disposition of the alicyclic chain into the smaller site (!).

It is still more difficult to apply the same model to the reduction of tetralone derived compounds, and particularly 2-tetralone-1-carboxyesters, because of the high hindrance of the aromatic group, the expected unsuitable arrangement of which in the model theoretically precluding any reduction.

It is thus necessary to build another model to explain the good yields and highly stereospecific results obtained in the reduction of tetralone carboxyesters by baker's yeast. We started from previous results showing that the reduction of 7-methoxy-2-carboxyethyl-1-tetralone **9** afforded exclusively a 1(*S*)-hydroxyester [53], despite the fact that a substrate with an equatorial 2-carboxyethyl group would present to the enzyme a carbonyl group with two nearly equivalent faces (Scheme 5), and thus may accommodate in the reducing site in an undifferentiated disposition. On the contrary, the preferred accommodation of the ketoester with an axial carboxyester (which indeed is the energetically favored conformation) would allow a better differentiation in the carbonyl faces recognition. Moreover, the attack of the carbonyl group by hydride on the opposite face to the carboxylate is mechanistically favored.



Scheme 5

We propose a more elaborate model (Figure 3), accounting for this carboxylate disposition, the acceptance of any position of the aromatic ring relative to the carbonyl group, and the stereochemical results observed. In such a model, the NAD(P)H site is situated below the carbonyl group, with the substrate lying in a flat, relatively narrow but extended cavity defined by the whole space occupied by the different tetralone-derived carboxyesters reduced, and with a free upper space corresponding to an axial carboxyester group . One

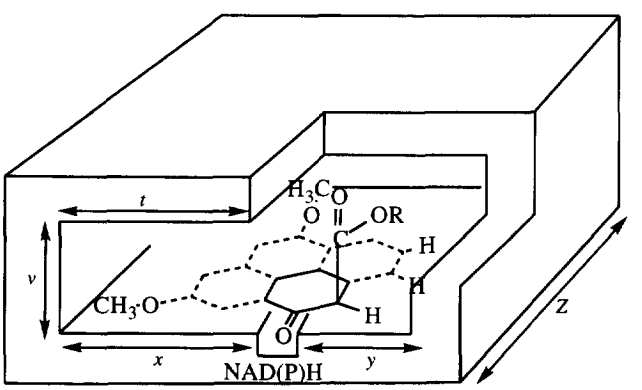
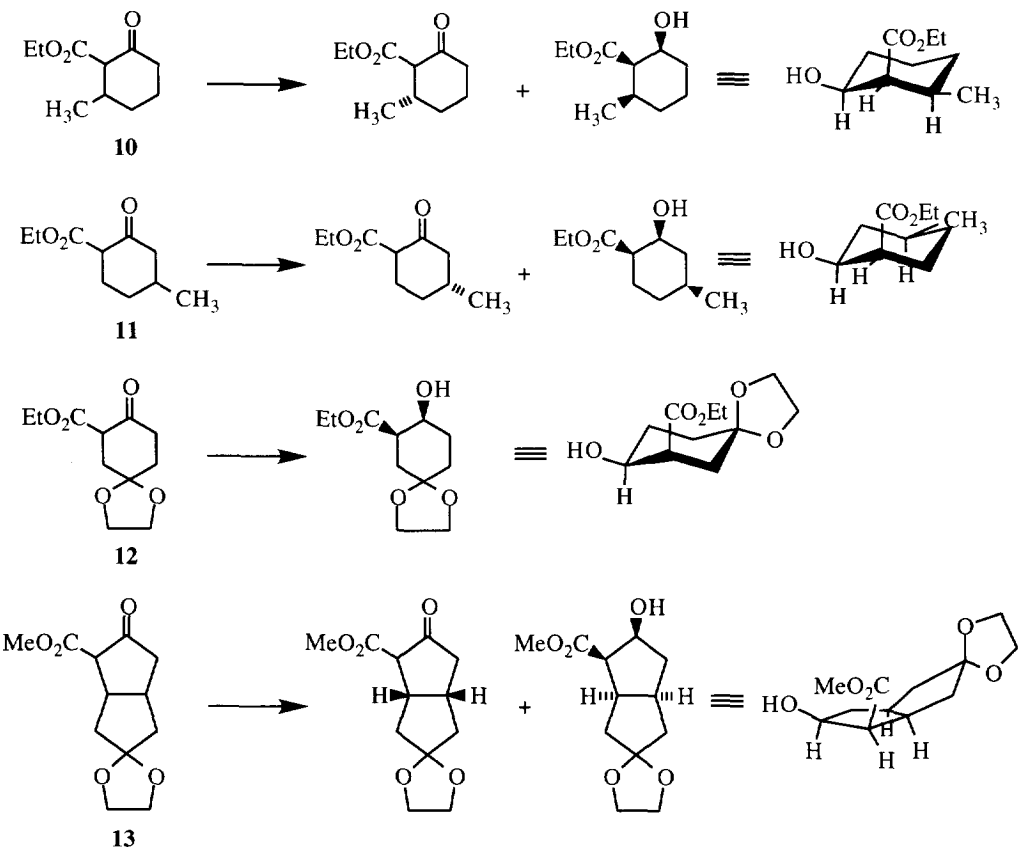


Fig. 3. Tentative schematic picture of a dehydrogenase active site model for the reduction of cyclic β-ketoesters by baker's yeast. The projection of a composite molecule, assuming the fitting of monocyclic and various tetralone substrates, has been visualized into the model, and defined by the following values corresponding to van der Waals surface boundaries: $v = 5.5$, $x \geq 8.5$, $y = 5$, $z \geq 9.5$, and $7.5 < t < 8.5$ Å.

can imagine that the disposition of the carboxyester group [63] is secured by a specific interaction with the active site, for example a hydrogen bond with some surrounding amino acid residue.

Such a model is compatible with all results reported in the literature for variously substituted cyclic β-ketoesters. For example, the reduction of ethyl 3-methylcyclohexanone-2 carboxylate **10** by baker's yeast has been reported to be highly enantioselective, only the 3*R*-ketoester being reduced to the corresponding 1*S*,2*R*,3*R*-hydroxyester [20]. Similarly, the 5*S*-isomer of ethyl 5-methylcyclohexanone-2 carboxylate **11** is mainly reduced to a 1*S*,2*R*,5*S*-hydroxyester [25,64]. In both cases, assuming an axial disposition of the carboxyester group of these substrates in our model, the observed enantiomeric specificity relative to the methyl group (resulting in substrate resolution) can be easily explained by the exclusive or major reduction of the isomer presenting an equatorial (in the plane) disposition of the methyl group (Scheme 6). An additional demonstration of the validity of the model may be found in the previously reported baker's yeast *cis* reduction of 4,4-ethylenedioxy-2-ethoxycarbonyl cyclohexanone **12** to an enantiomerically pure 1*R*,2*S* -hydroxyester [15,18], and the simultaneous resolution and stereoselective reduction of (±)-methyl (or ethyl) 3-oxo-7,7-(ethylenedioxy)-bicyclo[3.3.0]octane-2-carboxylate **13** to a 1*R*,2*R*,3*S*,5*S*-hydroxyester [16,17]. Both examples illustrate a relatively large space allowance above the ring plane, in a direction diametrically opposite to the carbonyl group.



Scheme 6

This model, which looks satisfactory for explaining the existing data obtained with baker's yeast or *S. montanus*, cannot be applied to the other microorganisms tested, such as *M. racemosus*, which is able to form a *trans* reduced product from the ketoester **4**.

CONCLUSION

We have shown that yeasts and fungi are able to readily reduce in good yields and sometimes with high complementary enantioselectivities the ketoesters derived from 1- or 2-tetralones, affording valuable asymmetric hydroxyester synthons. From the consistent stereochemical features observed with baker's yeast, it was possible to build a simple predictive model, which has now to be refined by extending the number and the structural variety of reducible cyclic β-ketoesters.

EXPERIMENTAL

Material and Methods.

All chemical used in synthetic procedures were reagent grade or better. 1-Carbomethoxy-2-tetralone **3** (bp 136-138°C/ 3 mm Hg) was obtained from 2-tetralone and dimethylcarbonate in the presence of sodium hydride [58]. 3-Carbomethoxy-2-tetralone **4** was obtained in 18% yield from 2-tetralone and a 2.5 N solution of magnesium methyl carbonate in DMF at 130°C, acidic hydrolysis and esterification with diazomethane [59]. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ with a Bruker WM250 instrument at 250.13 and 62.9 MHz, respectively, and chemical shifts, calibrated on the $CHCl_3$-$CDCl_3$ resonance, are reported in ppm, downfield from $(CH_3)_4Si$. GC-mass (GC-MS) data were obtained by electronic impact (EI) with a Hewlett-Packard 5890-II/5972 instrument equiped with a 25 m Ultra-1 capillary column. Optical rotations were measured using a Perkin Elmer 241C spectropolarimeter, in a 1 dm cell. X-ray crystallography was performed on an Enraf-Nonius CAD4 automatic diffractometer at University P. and M. Curie, Paris and structure was solved using the SHELLXS-86 program [61]. GC analyses were performed on a OV1701 (Pierce, 15 m x 0.20 mm) capillary column, with a flame ionization detector and helium (1 $kg.cm^{-2}$) as a carrier gas. Reactions were followed on Kieselgel $60F_{254}$ TLC plates, purchased from Merck. Visualization was achieved by UV inspection (254 nm), and by spraying with phosphomolybdic acid solution (5 g in 100 mL ethanol), followed by heating at about 120°C. Flash chromatography was realized either in glass column on Kieselgel 60 (Merck, 230-400 mesh), or using a Modulprep Jobin et Yvon system equiped with a 40 mm-diameter steel column, filled with Kieselgel 60H (Merck, 5-40 μm) at about 8 kg cm^{-1} pressure.

Microorganisms and cultures.

All cultures were maintained on agar slants containing (per litre), yeast extract (Difco) 5 g, Bacto-Peptone (Difco) 5 g, malt extract (Difco) 5 g, glucose 20 g and Bacto-agar (Difco) 20 g, stored at 4°C and subcultured before use. Fungi were purchased from the American Type Culture Collection (ATCC), Rockville, Md, USA, the Centraalbureau voor Schimmel Cultures (CBS), Baarn, the Netherlands, the Northern Regional Research Laboratories (NRRL), Peoria, Ill., USA, or the Quartermaster Research and Development Center, U.S.Army, Natick, Mass., USA.(QM). Some strains (no strain number) are from local origin. Screening experiments were realized by addition of the substrates (1 g L^{-1}) onto 65 h-old cultures of yeasts grown with orbital shaking (200 r.p.m.) at 27°C in 100 mL of a liquid medium containing (per litre), yeast extract (Difco) 5 g, Bacto-Peptone (Difco) 5 g, malt extract (Difco) 10 g, glucose 20 g. Fungi were similarly grown in a liquid medium containing (per litre), atomized corn steep (Solulys A, Roquette, France) 5 g, glucose 30 g, KH_2PO_4 1 g, K_2HPO_4 2 g, $NaNO_3$ 2 g, KCl 0.5 g, $MgSO_4,7H_2O$ 0.5 g, $FeSO_4,7H_2O$ 0.02 g. The substrate (1 g L^{-1}) was then added and incubation was continued at 27°C with orbital shaking. Samples (1-2 mL) were withdrawn at intervals, centrifuged, and the supernatants were microfiltered (0.45 μm). Aliquots of the filtrates were saturated with sodium chloride and extracted with ethyl acetate for GC analysis. Most transformations were continued until a total disappearance of substrate was observed (usually 1-4 days). Preparative experiments were similarly performed, in one or several 0.5-1 L-amounts.

Determination of diastereomeric and enantiomeric excesses.

Carbomethoxytetralones **3** and **4** were reduced with sodium borohydride at 0°C in methanol-water solution and the resulting extracted hydroxyesters were directly analyzed by GC (OV1701) for the separation of diasteromeric esters. Enantiomers separation was realized by GC (OV1701) after derivatisation with (*S*)-O-acetyllactyl chloride (≥ 98% e.e.) (Table 5)

Table 5. GC Separation of Diastereomeric and Enantiomeric Hydroxyesters Derived from **3** and **4**.

	Hydroxy esters			(*S*)-O-Acetyllactyl derivatives of enantiomeric hydroxyesters				
		cis	*trans*		*cis*		*trans*	
Substrate	Temperature	(min)	(min)	Temperature	(min)		(min)	
3	110-180°C (5°C/min)	15.5	17.12	160-190°C (1°C/min)	33.9	34.2	35.8	36.5
	then 10 min at 180°C			then 10 min at 190°C	(1*R*,2*S*)	(1*S*,2*R*)	(1*S*,2*S*)	(1*R*,2*R*)
4	110-180°C (2°C/min)	28.9	28.3	160-190°C (1°C/min)	34.6	35.9	37.3	36.5
				then 10 min at 190°C	(2*R*,3*S*)	(2*S*,3*R*)	(2*R*,3*R*)	2*S*,3*S*)

Methyl (1*R*,2*S*)-2-hydroxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate 5.

A solution of 1-carbomethoxy-2-tetralone **3** (1 g, 4.9 mmol) in EtOH-Tween 80 (8:2, 10 mL) was added to a 1 L-culture of *Rhizopus arrhizus* ATCC 11145. After 30 h incubation, the suspension was filtered, the filtrate was saturated with sodium chloride, filtered again with celite, then extracted 3 times with EtOAc. After drying and evaporation of the solvent, the crude residue was flash chromatographed (CH_2Cl_2-Et_2O, 9:1) to give **(1*R*,2*S*)-5** (0.55 g, 55% yield). Retention time (see Table 5); e.e 93%. $[\alpha]^{20}_D$ – 40 (c 1, $CHCl_3$); lit. (ethylester) [60] – 56. ^{1}H-NMR, δ ppm, J Hz: 1.95 (1H, m, H-3), 2.25 (1H, m, H-3), 2.85 (1H, m, H-4), 2.93 (1H, d, J = 6, OH), 3.05 (1H, dt, J = 6, 17.2, H-4), 3.75 (3H, s, OCH_3), 4.0 (1H, d, J = 5.2, H-1), 4.21 (1H, m, H-2), 7.0-7.2 (4H, m, H-5, -6, -7 and -8). ^{13}C-NMR, δ ppm: 26.93 and 27.88 (C-3, C-4), 50.31 (C-1), 52.15 (OCH_3), 67.84 (C-2), 125.98 and 127.32 (C-5, C-8), 129.06 and 129.59 (C-6, C-7), 131.60 and 136.17 (C-9, C-10), 173.76 (CO). EI.MS, m/z (relative abundance): 206(6) $[M]^+$, 188(13) $[M-H_2O]^+$, 147(9) $[M-CO_2Me]^+$, 129(100) $[M-77]^+$, 115(18) $[M-91]^+$.

Methyl (1*R*,2*R*)-2-hydroxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate 6.

A solution of 1-carbomethoxy-2-tetralone **3** (0.75g, 3.68 mmol) in EtOH-Tween 80 (8:2, 7.5ml) was added to a 750 mL-culture of *Aspergillus ochraceus* ATCC 1009. After 3 days incubation, the suspension was filtered, the filtrate was saturated with sodium chloride, filtered again with celite, then extracted 3 times with EtOAc. After drying and evaporation of the solvent, the crude residue was flash chromatographed (CH_2Cl_2-Et_2O, 91:9) to give **5** (0.247 g, 34% yield) and the desired **(1*R*,2*R*)-6** (0.105 g, 14% yield), mp 66°C (from cyclohexane). Retention time (see Table 5); e.e >98%. $[\alpha]^{20}_D$ + 17 (c 1, $CHCl_3$). ^{1}H-NMR, δ ppm, J Hz: 2.17 (2H, m, H-3), 2.91 (2H, dd, J = 5.2, 7.7, H-4), 3.80 (1H, d, J = 8, H-1), 3.78 (3H, s, OCH_3), 4.35 (1H, ddd, J = 3.4, J = 8.3, J = 10.5, H-2), 7.1-7.2 (4H, m, H-5, -6, -7 and -8). ^{13}C-NMR, δ ppm: 27.29 and 29.93 (C-3,C-4), 52.28 (C-1), 54.49 (OCH_3), 69.51 (C-2), 126.26 and 127.14 (C-5, C-8), 128.42 and 128.97 (C-6, C-7), 131.78 and 135.75 (C-9, C-10), 174.13 (CO). EI.MS, m/z (relative abundance): 206(6) $[M]^+$, 188(13) $[M-H_2O]^+$, 147(9) $[M-CO_2Me]^+$, 129(100) $[M-77]^+$, 115(18) $[M-91]^+$.

Absolute configuration of **6**: **(1*R*,2*S*)-5** was partially epimerized (about 70%) in CH_2Cl_2 solution (20 mg/2 mL) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (1% final concentration) at room temperature during 48 h. After derivatization with (*S*)-O-acetyllactyl chloride, GC on OV1701 column (see Table 5) showed a new peak with a 35.8 min retention time, corresponding to **(1*S*,2*S*)-6**.

Methyl (2*S*,3*S*)-3-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate 7.

A solution of 3-carbomethoxy-2-tetralone **4** (0.5 g, 2.45 mmol) in EtOH-Tween 80 (8:2, 5 mL) was added to a 0.5 L culture of *Mucor racemosus*. After 24 h incubation, the suspension was filtered, the filtrate was saturated with sodium chloride, filtered again with celite, then extracted 3 times with EtOAc. After drying and evaporation of the solvent, the crude residue was flash chromatographed (EtOAc-CH_2Cl_2, 9:1) to give **(2*S*,3*S*)-7** (0.384 g, 76% yield), mp 66°C (from pentane-Et_2O, 2:1). Retention time (see Table 5); e.e 94%. $[\alpha]^{20}_D$ + 135 (c 1, $CHCl_3$). ^{1}H-NMR, δ ppm, J Hz: 2.75 (1H, dd, J = 5.5, 11.8, H-1 or H-4), 2.8 (1H, dd, J = 5.5, 11.8, H-1 or H-4), 2.95 (1H, m, H-2), 3.1 (1H, d, J = 3.0, OH), 3.18 (2H, dd, J = 5.5, J = 16, H-4), 3.75 (3H, s, OCH_3), 4.25 (1H, tdd, J = 9.8, 5.5, 3, H-3), 7.0-7.2 (4H, m, H-5, -6, -7 and -8). ^{13}C-NMR, δ ppm: 31.70 and 37.00 (C-1, C-4), 47.73 (C-2), 52.06 (OCH_3), 68.26 (C-3), 126.25 and 126.35 (C-5, C-8), 128.24 and 129.12 (C-6, C-7), 133.58 and 133.95 (C-9, C-10), 175.13 (CO). EI.MS, m/z (relative abundance): 206(1) $[M]^+$, 188(22) $[M-H_2O]^+$, 129(100) $[M-77]^+$, 117(15) $[M-89]^+$, 115(16) $[M-91]^+$.

The absolute configuration of **7** was deduced from X-ray crystallographic analysis (Figure 1) of the corresponding **[(2*S*,3*S*)-3-carbomethoxy-1,2,3,4-tetrahydronaphthaleny-2-yl]-(1'*R*,4'*S*)-cam-phanate 9**. (2*S*,3*S*)-3-hydroxy-1,2,3,4-tetrahydronaphtalene-2-carboxylic acid methyl ester **(2*S*,3*S*)-7** (0.185 g, 0.9 mmol), (–)-camphanyl chloride (0.215 g, 1 mmol), pyridine (0.081 mL, 0.079 g, 1 mmol) and dimethylaminopyridine (2 mg) in CH_2Cl_2 (5 mL) were stirred during 16 h at room temperature. Ether (50 mL) was added. The mixture was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallized in pentane-ether to afford **9** (0.28 g, 77% yield). Crystals suitable for X-ray diffraction (Table 6) were obtained after recrystallization in a mixture of pentane-ether-CH_2Cl_2 (7:7:1), mp 120-122°C. ^{1}H-NMR, δ ppm, J Hz: 0.85, 0.95 and 1.05 (9H, 3s), 1.55-1.6 (1H, m), 1.75-1.9 (2H, m), 2.05-2.2 (1H, m), 2.85 (1H, dd, J = 8.8, 16.4), 3.0-3.2 (3H, m), 3.35 (1H, dd, J = 5.5, 16.4), 3.7 (3H, s), 5.55 (1H, dt, J = 8.8, 5.6), 7.05-7.15 (4H, m). ^{13}C-NMR, δ ppm: 9.62 (CH_3), 16.58 [$(CH_3)_2$], 28.83, 30.61, 31.17 and 33.79 (CH_2), 44.88 (C-2), 52.17 (OCH_3), 54.08 and 54.81 (C-1', CMe_2), 71.93 (C-1), 91.05 (C-4'), 126.61 (C-5, C-8), 128.23 and 128.91 (C-6, C-7), 132.34 and 132.98 (C-9, C-10), 166.59, 173.09 and 178.28 (CO).

Table 6. Crystal Parameters for the Camphanate Ester **9**

Formula	$C_{22}H_{26}O_6$
Mw	386.17
crystal system	monodimeric
space group	$P2_1$
a (Å)	6.938(2)
b (Å)	7.065(3)
c (Å)	20.624(4)
b (deg.)	90.53(2)
V (Å^3)	1011(2)
Z	2
R	0.08

Methyl (2*S*,3*R*)-3-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate 8.

A solution of 3-carbomethoxy-2-tetralone **4** (0.5 g, 2.45 mmol) in EtOH-Tween 80 (8:2, 5 mL) was added to a 0.5 L culture of *Sacharomyces montanus* CBS 6772. After 10 h incubation, the suspension was filtered, the filtrate was saturated with sodium chloride, filtered again with celite then extracted 3 times with EtOAc. After drying and evaporation of the solvent, the crude residue was flash chromatographed (AcOEt-CH_2Cl_2, 92:8) to give **(2*S*,3*R*)-8** (0.267 g, 53% yield). Retention time (see Table 5); e.e 77%. $[\alpha]^{20}_D$ – 18 (c 1, $CHCl_3$). ^{1}H-NMR, δ ppm, J Hz: 2.8-3.1 (5H, m, H-1 and H-4, H-2, OH), 3.25 (1H, dd, J= 11, 16, H-1 or H-4), 3.75 (3H, s, OCH_3), 4.53 (1H, m, H-3), 7.05-7.15 (4H, m, H-5, -6, -7 and -8). ^{13}C-NMR, δ ppm, 26.98 and 36.17 (C-1, C-4), 43.96 (C-2), 51.99 (OCH_3), 65.58 (C-1), 126.05 and 128.69 (C-5, C-8),

128.99 and 129.59 (C-6, C-7), 132.67 and 133.79 (C-9, C-10), 175.39 (CO). EI.MS, m/z (relative abundance): 206(1) $[M]^+$, 188(22) $[M-H_2O]^+$, 129(100) $[M-77]^+$, 117(15) $[M-89]^+$, 115(16) $[M-91]^+$.

Absolute configuration of **8**: **(2*S*,3*S*)-7** was partially epimerized (about 20%) in acetonitrile solution in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (1% final concentration) at 70°C during 48 h. After derivatization with (*S*)-O-acetyllactyl chloride, GC on OV1701 column (see Table 5) showed a new peak with a 35.9 min retention time, corresponding to **(2*S*,3*R*)-8**.

Methyl (2*R*,3*S*)-3-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate 8.

A solution of 3-carbomethoxy-2-tetralone **4** (0.3 g, 2.45 mmol) in EtOH-Tween 80 (8:2, 3 mL) was added to a 0.3 L culture of *Aspergillus ochraceus* ATCC 1009. After 20 h incubation, the suspension was filtered, the filtrate was saturated with sodium chloride, filtered again with celite, then extracted 3 times with EtOAc. After drying and evaporation of the solvent, the crude residue was flash chromatographed (AcOEt-CH_2Cl_2, 92:8) to give **(2*R*,3*S*)-8** (0.155 g, 51% yield). Retention time (see Table 5); e.e 85%. $[\alpha]^{20}_D$ + 21 (c 1, $CHCl_3$).

ACKNOWLEDGEMENTS

C. Abalain was recipient of a postdoctoral fellowship allocated by the Groupement de Recherche de Lacq (G.R.L., Elf-Aquitaine). We are indebted to M. Maurs for maintaining and growing most of the microorganisms used in this work.

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(*Received in UK* 29 *July* 1996)