Pergamon

Tetrahedron Vol. 51, No. 42, pp. 11531-11546, 1995
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0040-4020/95 $9.50+0.00

0040-4020(95)00715-6

Baker's Yeast Mediated Reduction of Aromatic Ring Substituted 2-Tetralones

Paolo Manitto, Giovanna Speranza*, Diego Monti, Gabriele Fontana and Elisa Panosetti

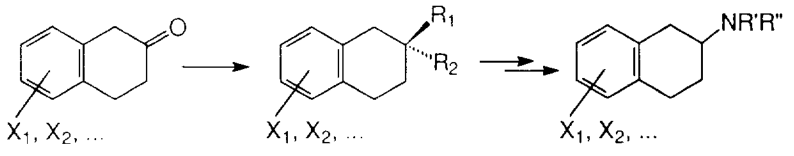
Dipartimento di Chimica Organica e Industriale, Università di Milano e Centro di Studio sulle Sostanze
Organiche Naturali, via Venezian 21, I-20133 Milano, Italy

Abstract : 2-Tetralones mono- and disubstituted with methoxy or hydroxy groups in the aromatic ring are hydrogenated to 2-tetralols in good yields by non-fermenting baker's yeast. The prevalent enantioform of the reduction product and its e.e. were found to depend on the substitution pattern. In one case, *i.e.* the biotransformation of 5-methoxy-2-tetralone into the corresponding 2-tetralol, an e.e. $\geq$ 98% was observed. A simple abstract model for explaining and predicting the stereochemical outcome in the yeast-mediated carbonyl reduction of 2-tetralones is proposed.

INTRODUCTION

Enantiomerically pure 2-tetralols (**2**) bearing hydroxy and/or alkoxy groups in the aromatic ring are of great synthetic importance since they can be converted easily into pharmacologically active 2-aminotetralin derivatives (**3**).[1] Hydroxy substituted *N*-alkylated 2-aminotetralins exhibit different degrees of activity on dopaminergic[2, 3] and serotonergic[2b] receptors, while methoxy 2-aminotetralins show affinity at the melatonin receptor.[4] A few glucosylated 2-tetralols have also been found in Nature.[5]

These facts and the well recognized possibility of obtaining optically pure secondary alcohols by microbial reduction of the corresponding ketones,[6] prompted us to investigate the baker's yeast mediated transformation of 2-tetralones (**1**) into 2-tetralols (**2**).



1 **2** **3**

$X_1, X_2, ... =$ OH, OMe

a : $R_1 =$ OH $R_2 =$ H
b : $R_1 =$ H $R_2 =$ OH

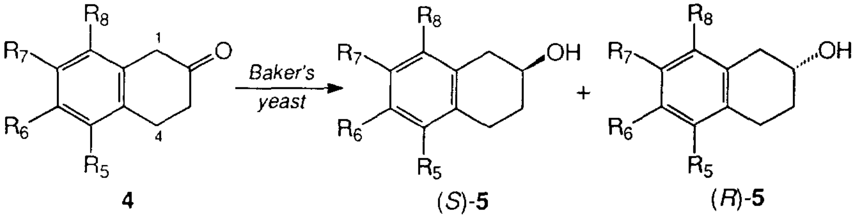
R', R" = H, alkyl

While the microbial reduction of hydroaromatic ketones has been largely investigated with regard to the 1-oxo derivatives,[7,8] much less attention has been addressed to 2-tetralones. 2-Tetralone (**1**, X_1, X_2 = H) has been reported to be converted into racemic and (*S*)-2-tetralol (**2a**, X_1, X_2 = H) by *Sporobolomyces pararoseus* and *Rhodotorula rubra*, respectively.[8] In addition, the ethyl esters of methoxy substituted 1,2,3,4-tetrahydro-

3-oxo-2-naphthoic and 1,2,3,4-tetrahydro-2-oxo-1-naphthoic acids were found to give the corresponding hydroxy esters with variable diastereo- and enantioselectivity when treated with non-fermenting baker's yeast.[9] We wish to report on : (1) the enantioselectivity in the reduction of 2-tetralones substituted with methoxy or hydroxy groups in the aromatic ring (**4a**-**k**) by action of baker's yeast (*Saccharomyces cerevisiae*) under "non-fermenting" conditions; (2) an interpretation of the apparent correlation between the prevalent enantioform of the 2-tetralol derivative and the substitution pattern of the starting ketone.

RESULTS

2-Tetralones. - 2-Tetralone (**4a**) and its 6-methoxy- (**4c**), 7-methoxy- (**4d**), and 6,7-dimethoxy- (**4g**) derivatives were commercially available. 5-Methoxy- (**4b**), 5,6-dimethoxy- (**4f**), 7,8-dimethoxy- (**4h**), and 5,8-dimethoxy-2-tetralone (**4i**) were obtained according to published procedures with modifications (see Experimental). 5-Hydroxy- (**4j**) and 8-hydroxy-2-tetralone (**4k**) were prepared from 6-methoxy- (**6a**) and 7-methoxy-1-tetralone (**6b**) respectively, as outlined in Scheme 1, *i. e.* by dehydrogenation over Pd/C in refluxing *p*-cymene,[10] followed by Birch reduction of the intermediate methoxy-1-naphthols (**7a,b**). In the same way, methylation of 7-methoxy-1-naphthol (**7b**) and subsequent reduction with sodium and alcohol, led to 8-methoxy-2-tetralone (**4e**).

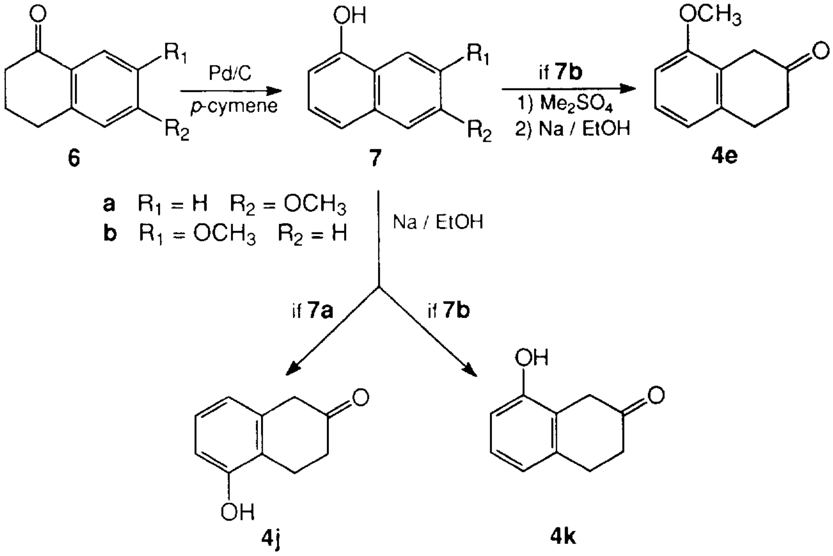


	R5	R6	R7	R8
a	H	H	H	H
b	OMe	H	H	H
c	H	OMe	H	H
d	H	H	OMe	H
e	H	H	H	OMe
f	OMe	OMe	H	H
g	H	OMe	OMe	H
h	H	H	OMe	OMe
i	OMe	H	H	OMe
j	OH	H	H	H
k	H	H	H	OH

Baker's yeast reduction of 2-tetralones. - The conversion of 2-tetralones (**4a-k**) into the corresponding 2-tetralols (**5a-k**) by *S. cerevisiae* was carried out under standard conditions [substrate (1g) added to a suspension of baker's yeast (100 g) in preboiled distilled water (1 L) at 37°C for 3-5 days]. Tetralols were isolated by flash chromatography of the ether extract of the reaction medium; the purity of all of them was checked by TLC (three eluents) and the structure confirmed by NMR spectroscopy.

The most abundant enantioform in tetralols **5a-e,g** and its excess were determined through RuO_4 catalyzed degradation[5a] to optically active β-methoxyadipic acid[11-13] (**8**) (Scheme 2) whose methyl ester[14] (**9**) was further analyzed by means of chiral gas chromatography. In the case of 2-tetralol (**5a**) the e.e. of the (*S*)-form, deduced as above, was found to be in excellent agreement with the value calculated by directly comparing its optical rotation with that reported for the enantiopure compound.[15]

Scheme 1

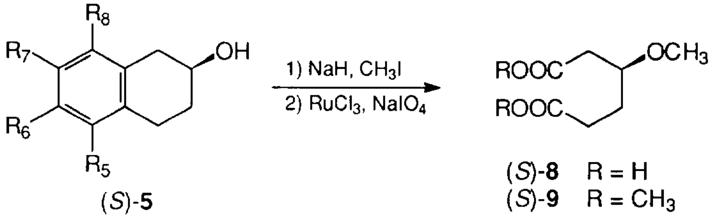


The enantiomeric composition of tetralols **5f,h,i** was obtained from the ^{19}F-NMR spectra of their esters with (*S*)-MPTA,[16] on the assumption that the CF_3 signal[17] at higher field was due to the (*R*)-tetralol derivative. This empirical rule was supported by a coherent correspondence between ^{19}F-chemical shift and the absolute configuration of C-2 in the Mosher's esters of the tetralols **5a-e,g**, whose e.e. had been measured independently *via* chemical correlation with methyl β-methoxyadipate (**9**).

Finally, 5- and 8-hydroxy-2-tetralols (**5j,k**) were converted into the methyl derivatives **5b** and **5e**, respectively, by treatment with dimethyl sulfate in order to determine their e.e.'s.

The results of all the biotransformation experiments are summarized in Table 1.

Scheme 2



DISCUSSION

It appears from the data of Table 1 that the baker's yeast catalyzed reduction of 2-tetralones having methoxy or hydroxy groups in the aromatic ring is characterized by a variable enantioselectivity with regard to the prevalent enantioform and its e.e. One relevant result is the conversion of the 5-methoxy derivative (**4b**) into the corresponding tetralol (*S*)-**5b** in almost enantiopure form.

Table 1. - Reduction of 2-tetralones using baker's yeast.

Entry	2-Tetralones (**4**)	2-Tetralols (**5**)		
		isolated yield %	prevalent enantioform	e.e. %
1	**a**	85	*S*	29
2	**b** (5-methoxy-)	87	*S*	≥98
3	**c** (6-methoxy-)	88	*S*	34
4	**d** (7-methoxy-)	92	*R*	38
5	**e** (8-methoxy-)	61	*R*	46
6	**f** (5,6-dimethoxy-)	79	*R*	59
7	**g** (6,7-dimethoxy-)	85	*R*	26
8	**h** (7,8-dimethoxy-)	87	*R*	46
9	**i** (5,8-dimethoxy-)	77	*R*	33
10	**j** (5-hydroxy-)	63	*S*	62
11	**k** (8-hydroxy-)	94	*S*	14

It is well known that low stereoselectivities shown by microbial-mediated biotransformations may be due essentially to two reasons:[6] *i*) a competition between two enzymes (or two families or enzymes), each having high but opposite stereochemical preference, and *ii*) the action of a single enzyme through different transition states resulting from the interaction of either the enantio- (or diastereo-) face of the substrate with the "chemical operator" of the biocatalyst.

The former situation, which was treated theoretically and experimentally by Sih *et al.*,[18] is typically revealed by the dependence of the e.e. of the product on the substrate concentration under physiological conditions (*i.e.* the substrate concentration being below saturation). Such a possibility was then tested in the case of the formation of 6-methoxy-2-tetralol (**5c**) from the corresponding ketone **4c**. The practically constant e.e. of (*S*)-**5c**, which was observed at complete conversion of the tetralone with substrate concentration ranging from 0.025 to 10 g/L (Table 2), is strongly indicative of the involvement of a single oxidoreductase.[18]

Supposing that the dehydrogenase involved allows an alternative fit for the substrate into the enzyme active site, a rationale has been developed which accounts for the e.e.'s reported in Table 1. This rationale rests on simple considerations arising from the inspection of Table 1, and on a number of reasonable assumptions. In fact, if one divides the methoxy-substituted tetralones into two groups according to the prevalence of the enantioform of the corresponding tetralol, it clearly appears that : *(i) there is a tendency of the hydrogen donor [most probably NAD(P)H] to approach the Re-face of the carbonyl group [giving rise to (S)-tetralols], which is reinforced by substitution at 5-position; (ii) this stereoselectivity is reversed when positions 7 and/or 8 are occupied; (iii) the case of 5,6-dimethoxytetralone (4f) seems to be an exception to statements (i) and (ii).* The two mirror image orientations of the tetralone molecule in the enzyme active site, each determining a diastereoisomeric transition state in the hydrogenation process, can be represented as in Fig. 1 and called *S*- and *R*- orientations with reference to the resulting configuration of C-2 in tetralols.

Table 2. - Enantiomeric excess (e.e.) of (*S*)-6-methoxy-2-tetralol (5c) with respect to the 6-methoxy-2-tetralone (4c) concentration.

Expt.	substrate conc. (g/L)	yeast conc. (g/L)	e.e. (%) of (*S*)-**5c**[a]
1	0.025	100	34.9
2	0.05	100	33.9
3	0.1	100	34.5
4	0.3	100	34.6
5	0.9	100	34.1
6	1.2	100	34.5
7	2.0	100	33.3
8	5.0	400	33.8
9	7.0	800	32.4
10	10.0	800	33.0

[a] Determined by chiral HPLC of the corresponding methyl ether after complete conversion of **4c** (3-5 days).

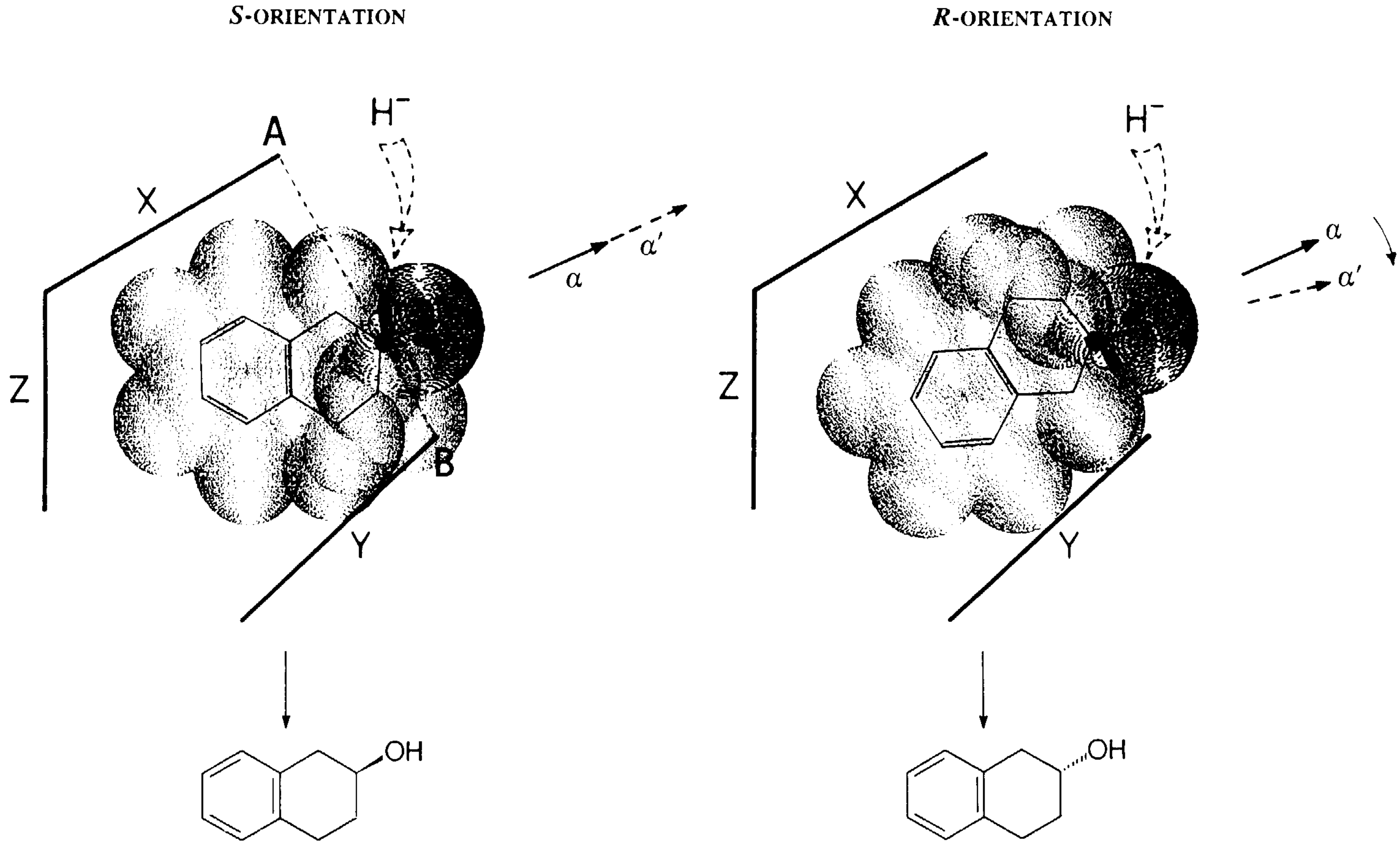
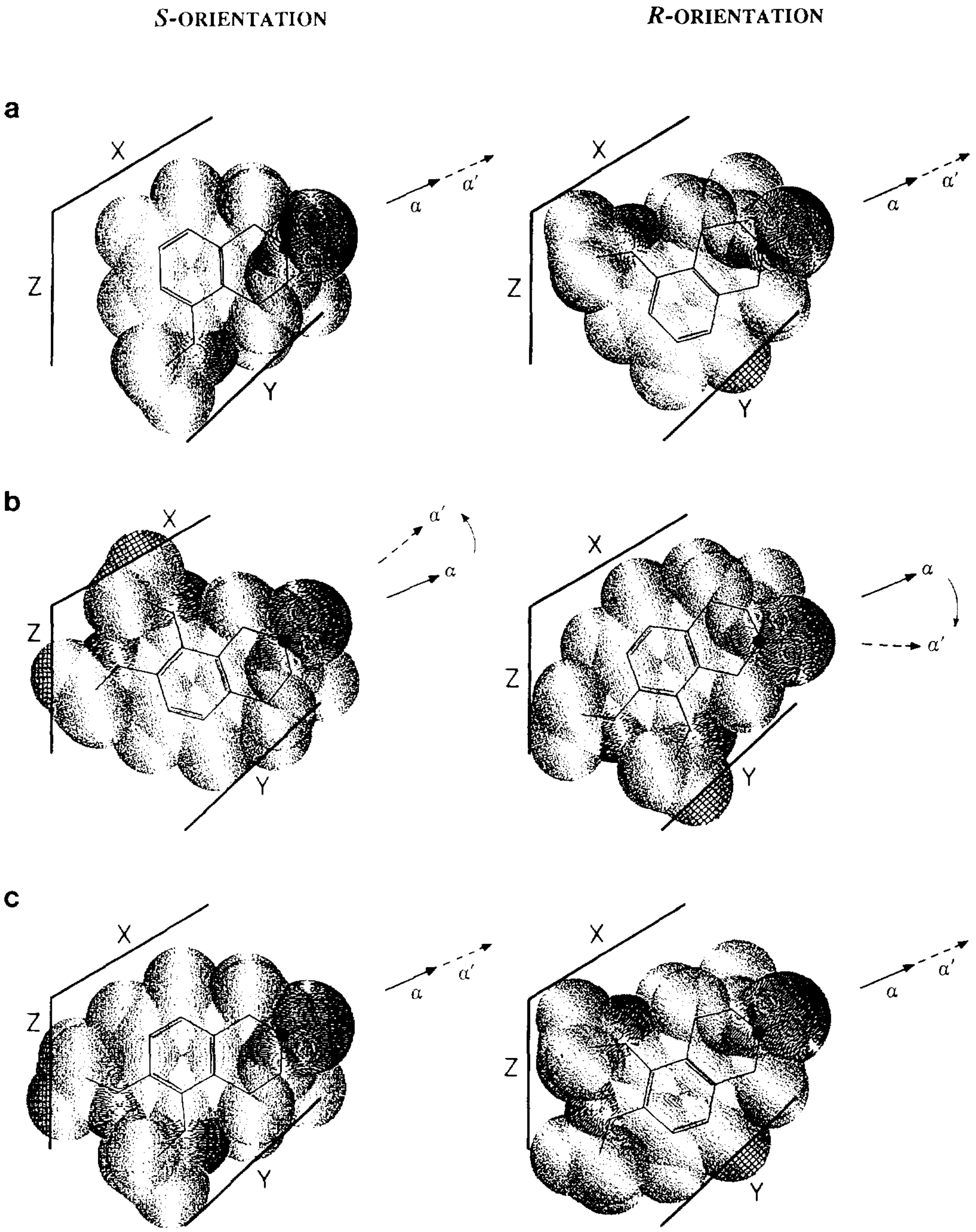


Figure 1. - Schematic representation of the 2-tetralol molecule (**4a**) (van der Waals surface) into a virtual enzyme active site. Coordinates of the enzyme-pocket model in arbitrary units, d (benzene C,C bond) : X,Y = 5d ; Z = 4d ; A-(C-2) = 4d ; C(2)-B = 2d ; $Z\hat{}X$ = 120° ; $X\hat{A}C(2)$ = 90° ; $Y\hat{B}C(2)$ = 115° ; $A\hat{C}(2)\alpha_{axis}$ = 95°.

Fig. 1 also shows a schematic picture of an ideal section of the enzyme pocket containing in its plane the nearly-planar molecular skeleton of 2-tetralone, three virtual active-site boundaries (X, Y, Z) involved in steric interactions with the guest molecule, and the preferred direction of the carbonyl group axis (α) with regard to the hydride transfer. The actual shape of the substrate molecule is visualized as van der Waals surface after minimization with MM2 force field. Van der Waals interactions between the hydrogen atoms of the aliphatic ring and the pocket boundaries are neglected. Thus, it is possible to estimate roughly the relative destabilizing interactions of the active site boundaries with molecules of differently substituted 2-tetralones lodged in each of the two opposite orientations (Fig. 2), on condition that the frame of the enzyme pocket, the position of C-2, and the direction of the α axis are kept unaltered (*cf.* caption of Fig. 1). It has been found that in methoxybenzenes the methyl group is in the plane of the aromatic ring, presumably because this favors overlap of the p-electrons of oxygen with π electrons of the ring.[19a] The free energy of two alternative transition states can be related to the destabilization of the *S*- and *R*-oriented "substrate in pocket". This destabilization will depend on the deviation angle formed by the "ideal" C=O axis (α) and that (α') adopted by the ketone molecule on rotation about C-2 to reduce steric interactions with X,Y,Z-boundaries, as well as residual interactions.

The preference for the formation of one enantiomer being inversely related to the energy of the corresponding transition state, the enantiomeric ratio of 2-tetralol (**5a**) (*S*/*R* = 65/35) can be explained considering the occurrence of an α, α' angle in the *R*-orientation (Fig. 1). In the case of substituted 2-tetralones (Fig. 2) a few additional assumptions are to be made concerning the direction assumed by the C=O axis (α') in order to minimize steric interactions, the extent of steric interaction of the substrate with pocket boundaries, and the rotameric preferences of methoxy groups. More pronounced destabilization of the transition state has to be associated with the rotation of the C=O axis from Y to X (ccw rotation) than with the opposite one (cw rotation) (this could be due to the existence of directional hydrogen bonds or metal ion complexation involving the carbonyl oxygen);[20] steric interactions with the Y-boundary are to be considered not as destabilizing as those with the other boundaries; finally, *O*-bonded methyl groups in 5- and 8-position are oriented far from the benzylic position 4 and 1 (because of 1,3-allylic strain),[19b] and, consequently, cause the O-CH_3 bond of the adjacent methoxy group to be directed towards 7- and 6-position, respectively. This assumption is consistent with theoretical and experimental data concerning the conformational preference of 1-methoxynaphthalene,[21] and is supported by ^{1}H NOE measurements [NOE enhancements (%), **4b** : from OCH_3 to H-6 (5.4), to CH_2-4 (not observed), from CH_2-4 to OCH_3 (not obs.); **4e** : from OCH_3 to H-7 (6.6), to CH_2-1 (not obs.), from CH_2-1 to OCH_3 (not obs.)]

Let us consider the single experiments of Table 1 using the 2-tetralone (**4a**) as a reference compound and the following order of destabilizing effects : overlaps with Z-boundary > X > Y > ccw α to α' > cw α to α'. The reason why *S*-selectivity in the reduction of 6-methoxy-2-tetralone (**4c**) is very close to that observed for **4a,** is that the 6-methoxy group, when directed towards the 5-position, does not modify steric interactions with respect to 2-tetralone in either of the two opposite orientations. The situation is different in the case of 5-methoxytetralone (**4b**) (*cf.* Figs. 1 and 2a) since a marked destabilization of the *R*-orientation, due to an overlap of 8-H with the Y-boundary, strongly favours the *S*-orientation: thus, almost enantiopure (*S*)-5-methoxy-2-tetralol is produced. The preference for the *R*-form found in **5d-i** (see in particular **4h** in Fig. 2b) would reflect the occurrence of an counterclockwise α to α' rotation in the *S*-orientation *vs.* a clockwise rotation in the *R*-orientation to reduce steric interactions of 8-, 7- and 7,8-methoxy groups with boundary X


S-ORIENTATION

R-ORIENTATION

Figure 2. - Representation of *S*- and *R*-oriented molecules of : (a) 5-methoxy-2-tetralone (**4b**); (b) 7,8-dimethoxy-2-tetralone (**4h**); (c) 6,7-dimethoxy-2-tetralone (**4g**).

and/or Z. In the case of 5,6-dimethoxy-2-tetralone (**4f**) (Fig. 2c) the reversed stereoselectivity with respect to the 5-methoxy-2-tetralone (**4c**) (Fig. 2a) can be explained taking account of the destabilizing effect on the *S*-orientation caused by the 6-methoxy group, which should have its O-CH_3 bond forced towards the 7-position as a result of the rotameric preference of the 5-OCH_3 (interactions being stronger with Z- than Y-boundary).

Finally, that both 5- (**4j**) and 8-hydroxytetralone (**4k**) give rise to the corresponding tetralols enriched in the *S*-form is understandable considering that the the smaller size of the OH group in comparison with the OCH_3 group causes less destabilization of the *R*-orientation in the case of **4j** (*S*/*R* = 81/19 *vs*. 99/1 for **4b**), and of the *S*-orientation in the case of **4k** (*S*/*R* = 57/43 *vs*. 27/73 for **4e**).

It can be noticed that the proposed model (Fig. 1) of the enzyme pocket consists of two parts separated by α-axis which are different in size, that limited by X-boundary being larger than the other. If one utilizes this model to accommodate the two ligands of a carbonyl group with the bulky substituent placed in the larger part, the stereoselectivity of the reduction process is in agreement with Prelog's rule,[22] which was found to be held in the reduction of aliphatic and aromatic ketones by fermenting baker's yeast.[6] In addition, when the model is applied to the baker's yeast reduction of the ethyl esters of methoxy substituted 1,2,3,4-tetrahydro-3-oxo-2-naphthoic and 1,2,3,4-tetrahydro-2-oxo-1-naphthoic acids, predictions are in agreement with experimental results reported by Seebach *et al.*[9]

CONCLUSION

The baker's yeast reduction of 2-tetralones, we have explored for enantioselectivity, does not seem to be of general synthetic value. However, two worthwhile facts can be pointed out : *i)* The production of enantiopure (*S*)-5-methoxy-2-tetralol (**5b**), which could be used as an intermediate in the synthesis of dopaminergic (*S*)- and (*R*)-5-hydroxy-2-aminotetralins [in particular (*S*)-5-hydroxy-2(di-*n*-propylamino)tetralin,[23] whose preparation, so far, has been performed *via* resolution of (±)-2-benzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene].[24] *ii)* The development of a simple abstract model for explaining the stereochemical outcome in the biotransformation of 2-tetralones into optically active 2-tetralols. This model might be tested with other cyclic ketones.

EXPERIMENTAL

Melting points are uncorrected (Büchi apparatus). TLC was performed on Si gel F_{254} precoated aluminum sheets (0.2 mm layer, Merck), using hexane - ethyl acetate (3 : 2) as eluent, unless otherwise stated; ethyl ether - petroleum ether (2 : 1) and CH_2Cl_2 - ethyl acetate (1 : 1) were used as additional eluents to check the purity of 2-tetralols. Silica gel (40-63 μm) from Merck was used for flash chromatography. ^1H (300.133 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded on a Bruker AC 300 instrument. The ^1H and ^{13}C chemical shifts were referenced to the solvent signal (7.25 and 77.00 ppm, and 3.30 and 49.00 ppm for $CDCl_3$ and CD_3OD, respectively). NOE difference experiments were performed by using standard Bruker software (DISNMR version 91). EIMS spectra were run on a VG 7070 EQ mass spectrometer operating at 70 eV. Optical rotations were measured in MeOH at 25°C on a Perkin Elmer 241 polarimeter. GC analyses were carried out on a Carlo Erba Model 4160 Gas Chromatograph equipped with a FID detector. HPLC was performed on a Waters Model 600 E liquid chromatograph with a 745 integrator and a 484 UV-visible variable-wavelength detector.

Baker's yeast was from Distillerie Italiane (S. Quirico-Trecasali, Parma, Italy). 2-Tetralone (**4a**) and its 6-methoxy- (**4c**), 7-methoxy- (**4d**), and 6,7-dimethoxy- (**4g**) derivatives were from Aldrich, while 5-methoxy-(**4b**) and 5,6-dimethoxy-2-tetralone (**4f**) were obtained according to ref. 25 and 3b, respectively.

7,8-dimethoxy-2-tetralone (**4h**) was prepared by the published procedure,[26] with the following modifications : a) The intermediate 1,2,7-trihydroxynaphthalene (1g, 5.7 mmol) was methylated with MeI (1.4 ml, 22.5 mmol) and NaH (650 mg, 21.6 mmol, 80% dispersion in mineral oil) in THF (42 mL) under N_2. The reaction mixture was heated at reflux for 6 h with stirring. After cooling to 0°C, the reaction mixture was quenched with water and conc. HCl and the product extracted with ethyl ether. The residue, obtained on concentration, was flash chromatographed eluting with ethyl ether-petroleum ether (2 : 1) to give 1.1 g of 1,2,7-trimethoxynaphthalene (91% yield) pure by TLC (R_f 0.60, eluent as above). b) Final purification of 7,8-dimethoxy-2-tetralone (**4h**) was carried out by flash chromatography (eluent petroleum ether with increasing proportions of EtOAc) followed by recrystallization from petroleum ether (10.5% overall yield). TLC, R_f 0.43 (ethyl ether-petroleum ether, 2 : 1); mp 75-76°C (lit.[27] 76°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (app t, 2H, $<J>$ = 6.8 Hz, H_2-3), 2.98 (app t, 2H, $<J>$ = 6.8 Hz, H_2-4), 3.57 (s, 2H, H_2-1), 3.78 and 3.84 (2xs, 2x3H, 7-OCH_3 and 8-OCH_3), 6.77 (d, 1H, J = 8.3 Hz) and 6.90 (d, 1H, J = 8.3 Hz) (H-5 and H-6); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 28.03 (t), 38.47 (2xt), 55.83 (q), 60.32 (q), 110.74 (d), 122.73 (d), 127.25 (s), 129.45 (s), 146.29 (s), 151.22 (s), 210.28 (s); EI MS m/z 206 (M^+, 100), 191 (25), 164 (80), 149 (60).

5,8-dimethoxy-2-tetralone (**4i**) was prepared according to ref. 28 with some modifications : a) 1,4-dihydroxynaphthalene was used as starting material and methylated as follows: a 1-litre three-necked flask equipped with a reflux condenser, a rubber septum and a magnetic stirrer bar, was connected to an atmosferic pressure hydrogenation apparatus and charged with 140 g of $Ba(OH)_2 \cdot H_2O$ 140 g, 190 mL of DMF and 2 g of Pd/C (10%). The resulting suspension was vigorously stirred and saturated with hydrogen. After cooling to 0°C, 1,4-dihydroxynaphthalene dissolved in 10 mL of DMF (5.34 g, 33.4 mmol) and freshly distilled dimethyl sulfate (48 mL) were added and the reaction mixture maintained at room temperature under hydrogen, cooling momentarily in ice if the reaction became too vigorous. After 7 h, the catalyst was removed by filtration and the filtrate concentrated to approximately one third volume under reduced pressure, diluted with water (200 mL) and continously extracted with ethyl ether. The ether extract was dried (Na_2SO_4) and evaporated to leave a yellow oil which was purified by flash chromatography (eluent, hexane - ethyl ether, 7 : 3) to give 1,4-dimethoxynaphthalene (4.8 g, 76% yield), pure by TLC (R_f 0.49, eluent as above). b) Oxidation of the intermediate 5,8-dimethoxy-2-tetralol to **4i** was performed following the Swern procedure,[29] and the title compound was obtained in 67% yield. Mp 98-99°C (lit.[28] 98.5-99°C); ^{1}H NMR as in ref. 30; ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 21.84 (t), 38.03 (2xt), 55.73 (2xq), 108.04 (d), 108.28 (d), 123.67 (s), 126.00 (s), 150.44 (s), 150.61 (s), 210.44 (s); EI MS m/z 206 (M^+, 100), 191 (32), 164 (75), 149 (50).

5-Hydroxy-2-tetralone (**4j**). - A mixture of 6-methoxy-1-tetralone (**6a**, 2 g, 11.3 mmol), 10% Pd/C (2.7 g) in dry *p*-cymene (100 mL) was heated to reflux under N_2 for 24 h.[10] After cooling, the suspension was filtered and the filtrate extracted with 1N NaOH (2 x 25 mL). The aqueous layer was acidified with 6N HCl

and extracted with ethyl ether (2 x 30 mL). The combined organic extracts were washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give 1.2 g (61% yield) of 6-methoxy-1-naphthol (**7a**) pure by TLC analysis (R_f 0.44, $CHCl_3$ - ethyl acetate, 20 : 1), which was used without further purification.[31]
A vigorously stirred refluxing solution of **7a** (1 g, 5.7 mmol) in absolute EtOH (30 mL) was flushed with N_2. Sodium (2 g), cut in little pieces, was added over a period of 30 min, at a rate sufficient to maintain a vigorous boiling. An additional 30 mL of absolute EtOH was added and refluxing was continued until all the sodium had dissolved (2 h). After cooling the reaction mixture was diluted with water (50 mL), acidified with conc. HCl and the solution concentrated under reduced pressure until only H_2O remained. This aqueous layer was extracted with ethyl ether (3 x 50 mL) and the combined ether extracts washed with water and dried over Na_2SO_4. The residue, obtained on concentration, was dissolved in 50 mL of EtOH-H_2O (1 : 1), then *p*-toluenesulfonic acid (100 mg) was added, and the resulting mixture refluxed for 30 min. After cooling to r.t. EtOH was removed under reduced pressure, water (25 mL) was added and the aqueous layer extracted with ethyl ether (2 x 50 mL). Drying of the combined organic phases over Na_2SO_4 and removal of the solvent provided 780 mg of a crude residue which was purified by flash chromatography eluting with petroleum ether - ethyl acetate (3 : 2). The resulting 5-hydroxy-2-tetralone (**4j**) (650 mg, 70% yield) was shown to be pure by TLC (eluent as above, R_f 0.30). Mp 156-159°C (lit.[32] mp 155-162°C); ^1H NMR (CD_3OD, 300 MHz) δ 2.45 (app t, 2H, <*J*> = 6.8 Hz, H_2-3), 3.04 (app t, 2H, <*J*> = 6.8 Hz, H_2-4), 3.39 (s, 2H, H_2-1), 6.59 (d, 1H, *J* = 7.6 Hz) and 6.67 (d, 1H, *J* = 8.0 Hz) (H-6 and H-8), 6.98 (app t, 1H, <*J*> = 7.8 Hz, H-7); ^{13}C NMR (CD_3D, 75.47 MHz) δ 22.36 (t), 39.30 (t), 46.09 (t), 114.61 (d), 120.73 (d), 125.00 (s), 128.83 (d), 136.74 (s), 155.69 (s), 214.50 (s); EI MS *m/z* 162 (M^+, 75), 133 (10), 120 (100).

8-Hydroxy-2-tetralone (**4k**). - 7-Methoxy-1-naphtol (**7b**) was prepared from 7-methoxy-1-tetralone (**6b**) as described above for 6-methoxy-1-naphthol (**7a**) in 63% yield. TLC : R_f 0.44 ($CHCl_3$ - ethyl acetate, 20 : 1).[33] **7b** was used to prepare the title compound as described above for 5-hydroxy-2-tetralone (**4j**); 69% yield; mp 154-155°C (lit.[34] 156-157°C); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.95 (app t, 2H, <*J*> = 6.8 Hz, H_2-3), 3.05 (app t, 2H, <*J*> = 6.8 Hz, H_2-4), 3.57 (s, 2H, H_2-1), 5.05 (brs, 1H, 8-OH), 6.70 (d, 1H, *J* = 7.8 Hz) and 6.79 (d, 1H, *J* = 7.8 Hz) (H-5 and H-7), 7.06 (app t, 1H, <*J*> = 7.8 Hz, H-6); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 28.71 (t), 37.90 (t), 38.76 (t), 113.22 (d), 119.99 (d), 123.26 (s), 127.31 (d), 137.89 (s), 153.16 (s), 211.59 (s); EI MS *m/z* 162 (M^+, 60), 133 (20), 120 (100).

8-Methoxy-2-tetralone (**4e**). - 7-Methoxy-1-naphthol (**7b**) (1g, 5.7 mmol) was methylated with dimethyl sulphate (2 mL) and anhydrous K_2CO_3 (5 g) in dry acetone (100 mL). Usual work-up and purification by flash chromatography (eluent hexane - ethyl acetate, 5 : 1) gave 1,7-dimethoxynaphthalene[4] (84% yield), which was reduced to **4e** as previously described for 5-hydroxy-2-tetralone (**4j**). The spectral data were in close agreement with those published.[4, 34]

General procedure for biotransformations. - A suspension of baker's yeast (100 g) in preboiled distilled water (1 L) was kept at 37°C for 30 min. Then the substrate (1g), dissolved in 10 mL of EtOH, was gradually added and the mixture vigorously stirred for 3-5 days at 37°C. Progress of the reduction was monitored by TLC analysis. When reaction was complete, the product was continously extracted with ethyl ether. The ether extract was dried (Na_2SO_4), evaporated under reduced pressure and purified by flash chromatography eluting with hexane-ethyl acetate to afford pure samples of 2-tetralols (see Table 1 for yields and e.e.'s).

2-Tetralol (**5a**). - TLC, R_f 0.49; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75-1.88 (m, 1H, H-3_a), 1.99-2.10 (m, 2H, H-3_b and OH), 2.77 (dd, 1H, J = 16.2 and 7.8 Hz, H-1_a), 2.80-3.01 (m, 2H, H_2-4), 3.08 (dd, 1H, J = 16.2 and 4.9 Hz, H-1_b), 4.11-4.19 (m, 1H, H-2), 7.06-7.16 (m, 4H, arom. H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.94 (t), 31.41 (t), 38.30 (t), 67.09 (d), 125.83 (d), 125.95 (d), 128.56 (d), 129.48 (d), 134.19 (s), 135.62 (s); EI MS *m/z* 148 (M^+, 25), 130 (100), 104 (70); $[\alpha]_D^{25}$ - 20.8 (*c* 0.25, 29% ee) (lit.[15] -72.2, *c* 1.61, EtOH).

5-Methoxy-2-tetralol (**5b**). - TLC, R_f 0.54; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 1H, OH), 1.71-1.83 (m, 1H, H-3_a), 2.00-2.10 (m, 1H, H-3_b), 2.65 (ddd, 1H, J = 17.9, 8.3 and 6.9 Hz, H-4_a), 2.75 (dd, 1H, J = 16.2 and 8.4 Hz, H-1_a), 2.90 (app dt, 1H, J = 17.9 and <J> = 5.7 Hz, H-4_b), 3.05 (dd, 1H, J = 16.2 and 4.5 Hz, H-1_b), 3.80 (s, 3H, 5-OCH_3), 4.07-4.16 (m, 1H, H-2), 6.67 (d, 1H, J = 7.9 Hz) and 6.69 (d, 1H, J = 7.9 Hz) (H-6 and H-8), 7.00 (app t, 1H, <J> = 7.9 Hz, H-7); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 21.14 (t), 30.95 (t), 38.33 (t), 55.18 (q), 67.00 (d), 107.20 (d), 121.59 (d), 124.47 (s), 126.40 (d), 135.56 (s), 157.09 (s); EI MS *m/z* 178 (M^+, 81), 160 (100), 145 (47), 134 (60); $[\alpha]_D^{25}$ - 53.3 (*c* 0.35, ≥ 98% ee).

6-Methoxy-2-tetralol (**5c**). - TLC, R_f 0.41; ^{1}H NMR data as in ref. 35; ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 27.22 (t), 31.33 (t), 37.57 (t), 55.20 (q), 67.36 (d), 112.21 (d), 113.15 (d), 126.21 (s), 130.29 (d), 136.68 (s), 157.76 (s); EI MS *m/z* 178 (M^+, 76), 160 (60), 145 (22), 134 (100); $[\alpha]_D^{25}$ - 16.1 (*c* 0.22, 34% ee).

7-Methoxy-2-tetralol (**5d**). - TLC, R_f 0.40; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (s, 1H, OH), 1.73-1.87 (m, 1H, H-3_a), 1.98-2.08 (m, 1H, H-3_b), 2.70-2.81 (m, 2H, H-1_a and H-4_a), 2.88 (app dt, 1H, J = 16.7 and <J> = 5.9 Hz, H-4_b), 3.05 (dd, 1H, J = 16.3 and 4.7 Hz, H-1_b), 3.76 (s, 3H, 7-OCH_3), 4.09-4.19 (m, 1H, H-2), 6.61 (d, 1H, J = 2.6 Hz, H-8), 6.69 (dd, 1H, J = 8.4 and 2.6 Hz, H-6), 7.00 (d, 1H, J = 8.4 Hz, H-5); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.07 (t), 31.67 (t), 38.60 (t), 55.24 (q), 67.20 (d), 112.37 (d), 113.93 (d), 127.70 (s), 129.45 (d), 135.34 (s), 157.69 (s); EI MS *m/z* 178 (M^+, 74), 160 (100), 145 (46), 134 (66); $[\alpha]_D^{25}$ + 16.3 (*c* 0.23, 38% ee).

8-Methoxy-2-tetralol (**5e**). - TLC, R_f 0.46; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73-1.85 (m, 1H, H-3_a), 1.97-2.06 (m, 1H, H-3_b), 2.14 (s, 1H, OH), 2.56 (dd, 1H, J = 17.1 and 7.5 Hz, H-1_a), 2.81 (ddd, 1H, J = 16.9, 8.5 and 6.0 Hz, H-4_a), 2.94 (app dt, 1H, J = 16.9 and <J> = 5.4 Hz, H-4_b), 3.08 (dd, 1H, J = 17.1 and 5.0 Hz, H-1_b), 3.81 (s, 3H, 8-OCH_3), 4.09-4.17 (m, 1H, H-2), 6.67 (d, 1H, J = 8.0 Hz) and 6.73 (d, 1H, J = 7.6 Hz) (H-5 and H-7), 7.10 (app t, 1H, <J> = 7.8 Hz, H-6); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.98 (t), 30.87 (t), 32.34 (t), 55.15 (q), 67.06 (d), 106.98 (d), 120.72 (d), 123.16 (s), 126.16 (d), 137.00 (s), 157.46 (s); EI MS *m/z* 178 (M^+, 70), 160 (80), 145 (25), 134 (100); $[\alpha]_D^{25}$ + 27.5 (*c* 0.35, 46% ee).

5,6-Dimethoxy-2-tetralol (**5f**). - TLC, R_f 0.33; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68-1.80 (m, 1H, H-3_a), 1.97-2.08 (m, 2H, H-3_b and OH), 2.68 (dd, 1H, J = 15.9 and 8.2 Hz, H-1_a), 2.70-2.78 (m, 1H, H-4_a), 2.94-3.04 (m, 2H, H-1_b and H-4_b), 3.79 and 3.82 (2xs, 2x3H, 5-OCH_3 and 6-OCH_3), 4.03-4.12 (m, 1H, H-2), 6.73 (d, 1H, J = 8.4 Hz) and 6.78 (d, 1H, J = 8.4 Hz) (H-7 and H-8); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 21.30 (t), 30.85 (t), 37.70 (t), 55.78 (q), 59.80 (q), 67.00 (d), 110.52 (d), 124.44 (d), 127.47 (s), 129.89 (s), 146.32 (s), 150.49 (s); EI MS *m/z* 208 (M^+, 100), 190 (55), 175 (40), 159 (25); $[\alpha]_D^{25}$ + 39.7 (*c* 0.42, 59% ee).

6,7-Dimethoxy-2-tetralol (**5g**). - TLC, R_f 0.20; spectral data matched those reported in ref. 36; $[\alpha]_D^{25}$ + 17.7 (*c* 0.35, 26% ee).

7,8-Dimethoxy-2-tetralol (**5h**). - TLC, R_f 0.66; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69-1.82 (m, 2H, H-3_a and OH), 1.96-2.03 (m, 1H, H-3_b), 2.64 (dd, 1H, *J* = 17.0 and 7.7 Hz, H-1_a), 2.75 (ddd, 1H, *J* = 16.6, 8.9 and 5.8 Hz, H-4_a), 2.88 (app dt, 1H, *J* = 16.6 and <*J*> = 5.7 Hz, H-4_b), 3.15 (dd, 1H, *J* = 17.0 and 5.1 Hz, H-1_b), 3.79 and 3.82 (2xs, 2x3H, 7-OCH_3 and 8-OCH_3), 4.07-4.16 (m, 1H, H-2), 6.73 (d, 1H, *J* = 8.4 Hz) and 6.80 (d, 1H, *J* = 8.4 Hz) (H-5 and H-6); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.36 (t), 31.26 (t), 32.69 (t), 55.92 (q), 59.96 (q), 67.17 (d), 110.65 (d), 123.68 (d), 128.76 (s), 128.93 (s), 146.91 (s), 150.53 (s); EI MS *m/z* 208 (M^+, 100), 190 (75), 175 (60), 159 (40); $[\alpha]_D^{25}$ + 18.1 (*c* 0.41, 46% ee).

5,8-Dimethoxy-2-tetralol (**5i**). - TLC, R_f 0.46; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 1H, OH), 1.69-1.81 (m, 1H, H-3_a), 1.95-2.05 (m, 1H, H-3_b), 2.55 (dd, 1H, *J* = 17.1 and 7.3 Hz, H-1_a), 2.64 (ddd, 1H, *J* = 17.8, 8.6 and 6.9 Hz, H-4_a), 2.90 (app dt, 1H, *J* = 17.8 and <*J*> = 5.8 Hz, H-4_b), 3.05 (dd, 1H, *J* = 17.1 and 5.0 Hz, H-1_b), 3.77 (s, 6H, 5-OCH_3 and 8-OCH_3), 4.15-4.18 (m, 1H, H-2), 6.62 (s, 2H, H-6 and H-7); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 21.31 (t), 30.28 (t), 32.51 (t), 55.51 (2xq), 66.72 (d), 107.00 (2xd), 124.65 (s), 126.03 (s), 151.13 (s), 151.45 (s); EI MS *m/z* 208 (M^+, 100), 190 (40), 175 (54), 164 (31), 159 (25); $[\alpha]_D^{25}$ + 20.1 (*c* 0.45, 33% ee).

5-Hydroxy-2-tetralol (**5j**). -TLC, R_f 0.26; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.61-1.75 (m, 1H, H-3_a), 1.98-2.08 (m, 1H, H-3_b), 2.52-2.69 (m, 2H, H-1_a and H-4_a), 2.87 (app dt, 1H, *J* = 17.6 and <*J*> = 5.8 Hz, H-4_b), 2.96 (dd, 1H, *J* = 16.6 and 4.9 Hz, H-1_b), 3.92-4.01 (m, 1H, H-2), 6.53 (d, 1H, *J* = 7.8 Hz) and 6.54 (d, 1H, *J* = 7.8 Hz) (H-6 and H-8), 6.88 (app t, 1H, <*J*> = 7.8 Hz); ^{13}C NMR (CD_3OD 75.47 MHz) δ 22.48 (t), 32.17 (t), 39.23 (t), 67.95 (d), 112.82 (d), 121.54 (d), 123.92 (s), 127.27 (d), 137.14 (s), 155.74 (s); EI MS *m/z* 164 (M^+, 70), 146 (100), 131 (45), 120 (86); $[\alpha]_D^{25}$ - 46.3 (*c* 0.40, 62% ee).

8-Hydroxy-2-tetralol (**5k**). - TLC, R_f 0.21; ^{1}H NMR (CD_3OD 300 MHz) δ 1.62-1.75 (m, 1H, H-3_a), 1.91-1.98 (m, 1H, H-3_b), 2.46 (dd, 1H, *J* = 16.9 and 8.0 Hz, H-1_a), 2.68-2.90 (m, 2H, H_2-4), 3.03 (dd, 1H, *J* = 16.9 and 5.1 Hz, H-1_b), 3.96-4.03 (m, 1H, H-2), 6.53 (d, 1H, *J* = 7.7 Hz) and 6.55 (d, 1H, *J* = 7.7 Hz) (H-5 and H-7), 6.87 (app t, 1H, <*J*> = 7.7 Hz, H-7); ^{13}C NMR (CD_3OD, 75.47 MHz) δ 28.88 (t), 32.80 (t), 33.66 (t), 68.71 (d), 113.10 (d), 121.16 (d), 123.31 (s), 127.59 (d), 138.75 (s), 156.67 (s); EI MS *m/z* 164 (M^+, 80), 146 (100), 131 (53), 120 (86); $[\alpha]_D^{25}$ - 10.8 (*c* 0.32, 14% ee).

General procedure for degradation of 2-tetralols (5a-k). - A stirred suspension of NaH (4 mmol, 120 mg of 80% dispersion in mineral oil) in dry THF (3 mL) was heated at 45-55°C under N_2 and treated with methyl iodide (0.3 mL, 4.5 mmol). 2-Tetralol (3 mmol) dissolved in 1.5 mL of dry THF was added dropwise over 15 min and the resulting mixture heated at 50°C for 4h. This mixture was then cooled to r.t., quenched by addition of water (10 mL), acidified with 2N HCl and extracted with ethyl ether (3 x 50 mL). The organic extracts were combined, washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue which was flash chromatographed (eluent hexane-ethyl acetate) to give the methyl ethers of 2-tetralols in 90-95% yields.

The above methyl ethers (2.5 mmol) were subjected to RuO_4 catalyzed oxidation as described in ref. 5a. The resulting β-methoxyadipic acid (**8**)[12, 13] was converted into its dimethyl ester (**9**)[14] by treatment with an ethereal solution of CH_2N_2 and analyzed by chiral GC. Chromatographic resolution of the enantiomers of dimethyl β-methoxyadipate (**9**) was achieved with a fused silica capillary column (25 m x 0.25 mm i.d.) coated with 2,6-dimethyl-3-trifluoroacetyl-γ-cyclodextrin/OV 1701 (5%) (film thickness 0.15 µm). Operating conditions : injector, 220 °C; FID, 250 °C; oven, from 70 to 170 °C at 2 °C/min and kept at 170 °C for 10 min; carrier gas, H_2 at 45 cm/sec. Retention times of the (*S*)- and (*R*)-enantiomer were 33.3 and 34.0 min, respectively. These assigments were based on the known enantiomeric composition of a sample of β-methoxyadipic acid, as determined by optical rotation measurements.[12, 13]

Preparation and analysis of MTPA esters. - The (*S*)-MTPA esters of tetralols **5a-k** were prepared from commercially available (*R*)-(-)-MTPA-Cl, according to the procedure described in ref. 16. Usually 10 mg of 2-tetralol was used. ^{19}F NMR spectra were measured in $CDCl_3$ at 282.40 MHz with $CFCl_3$ as internal standard. Ranges of chemical shifts (ppm) : from - 71.29 to - 71.39 δ for (*S*, *S*)-esters; from - 71.46 to - 71.56 δ for (*R*, *S*)-esters; δ(*S*, *S*) - δ(*R*, *S*) : from 0.14 to 0.17 ppm.

Reduction of 6-methoxy-2-tetralone (4c) at different substrate concentrations. - Microbial reduction of **4c** at concentrations ranging from 0.025 to 10.0 g/L was carried out as previously described (see Table 2). After extraction with ethyl ether, the crude 6-methoxy-2-tetralol (**5c**) was treated with methyl iodide and NaH in THF (as described for degradation of 2-tetralols) giving the corresponding methyl ether : TLC, R_f 0.70; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.73-1.86 (m, 1H, H-3_a), 2.00-2.10 (m, 1H, H-3_b), 2.70 (dd, 1H, J = 16.0 and 7.9 Hz, H-1_a), 2.75-2.95 (m, 2H, H_2-4), 3.00 (dd, 1H, J = 16.0 and 4.7 Hz, H-1_b), 3.41 (s, 3H, 2-OCH_3), 3.59-3.67 (m, 1H, H-2), 3.76 (s, 3H, 6-OCH_3), 6.62 (d, 1H, J = 2.6 Hz, H-5), 6.69 (dd, 1H, J = 8.3 and 2.6 Hz, H-7), 6.99 (d, 1H, J = 8.3 Hz, H-8). The optical purity of this methyl ether and, as a consequence, of the starting **5c** was determined by HPLC analysis using a CHIRALCEL OB (250 x 4.6 mm, Daicel) column. Chromatographic conditions : flow rate, 0.9 mL/min; eluent, hexane-2-propanol (94 : 6); detector, λ 210 nm; measurements were carried out at room temperature. Retention times of (*R*)- and (*S*)-enantiomer were found to be 6.6 and 9.1 min, respectively, the elution order having been determined by chromatographing a sample of known enantiomeric composition under the same conditions.

ACKNOWLEDGEMENTS

We thank A. Bravo for technical assistance and MURST (Italy) for financial support.

REFERENCES

1. Casy, A. F. *The Steric Factor in Medicinal Chemistry: Dissymmetric Probes of Pharmacological Receptors*; Plenum Press: New York, 1993.
2. a) Alkorta, I.; Villar, H. O. *J. Med. Chem.* **1994**, *37*, 210-213 and refs. cited therein; b) Liu, Y.; Yu, H.; Mohell, N.; Nordvall, G.; Lewander, T.; Hacksell, U. *J. Med. Chem.* **1995**, *38*, 150-160 and refs cited therein.
3. a) Castelnovo, P. *Chirality* **1993**, *5*, 181-187 and refs cited therein; b) Copinga, S.; Dijkstra, D.; de Vries, J. B.; Grol, C. J.; Horn, A. S. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 137-142.
4. Copinga, S.; Tepper, P. G.; Grol, C. J.; Horn, A. S.; Dubocovich, M. L. *J. Med. Chem.* **1993**, *36*, 2891-2898.
5. a) Speranza, G.; Manitto, P.; Pezzuto, D.; Monti, D. *Chirality* **1991**, *3*, 263-267; b) Speranza, G.; Manitto, P.; Monti, D.; Pezzuto, D. *J. Nat. Prod.* **1992**, *55*, 723-729; c) Kurokawa-Nose, Y.; Shimada, T.; Wada, H.; Tanaka, N.; Murakami, T.; Saiki, Y. *Chem. Pharm. Bull.* **1993**, *41*, 930-932.
6. Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, 1992; pp.149-168.
7. Kabuto, K.; Imuta, M.; Kempner, E. S.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 2357-2361.
8. Bégué, J.-P.; Cerceau, C.; Dogbeavou, A.; Mathé, L.; Sicsic, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3141-3144.
9. Seebach, D.; Roggo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta* **1987**, *70*, 1605-1615.
10. Newman, M. S.; Blum, J. *J. Am. Chem. Soc.* **1964**, *86*, 503-507.
11. Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1949**, *32*, 1613-1617.
12. Viscontini, M.; Miglioretto, P. *Helv. Chim. Acta* **1955**, *38*, 930-935.
13. Brenneisen, K.; Tamm, C.; Reichstein, T. *Helv. Chim. Acta* **1956**, *39*, 1233-1241.
14. Akhtar, M. N.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 676-678.
15. Arakawa, H.; Torimoto, N., Masui, Y. *Liebigs Ann. Chem.* **1969**, *728*, 152-157.
16. Dale, J. A.; Dull, D. L., Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.
17. a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147; b) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203-10213.
18. Chen, C.-S.; Zhou, B.-N., Girdaukas, G.; Shieh, W.-R., VanMiddlesworth, F.; Gopalan, A. S.; Sih, C. J. *Bioorg. Chem.* **1984**, *12*, 98-117.
19. a) Eliel, E. E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley : New York, 1994; p. 627; b) *ibidem*, pp. 737-740.
20. Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman: San Francisco, 1979; pp. 324-325.
21. Salman, S. R. *Magn. Res. in Chemistry* **1985**, *23*, 119-121.
22. Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119-130.
23. Seiler, M. P.; Stoll, A. P.; Closse, A.; Frick, W.; Jaton, A.; Vigouret, J.-M. *J. Med. Chem.* **1986**, *29*, 912-917.
24. McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547-549.

25. Cordi, A. A.; Lacoste, J.-M.; Hennig, P. *J. Chem. Soc., Perkin Trans. 1* **1993,** 3-4.
26. Soffer. M. D.; Stewart, R. A.; Cavagnol, J. C.; Gellerson, H. E., Bowler, E. A. *J. Am. Chem. Soc.* **1950,** *72,* 3704-3709.
27. Diamond, G. B.; Soffer, M. D. *J. Am. Chem. Soc.* **1952,** *74,* 4126-4127.
28. Arvidsson, L.-E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L. G.; Lindberg, P.; Sanchez, D.; Wikström, H., Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1984,** *27,* 45-51.
29. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978,** *43,* 2480-2482.
30. Perez, F.; Rosell, G.; Mauleon, D.; Carganico, G. *Farmaco, Ed. Sci.* **1991,** *46,* 1155-1166.
31. Chatterjee, A.; Raychaudhuri, S. R.; Chatterjee, S. K. *Tetrahedron* **1981,** *37,* 3653-3660.
32. Eastham, J. F.; Larkin, D. R. *J. Am. Chem. Soc.* **1958,** *80,* 2887-2893.
33. Bell, K. H.; McCaffery, L. F. *Aust. J. Chem.* **1993,** *46,* 731-737.
34. Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1974,** *27,* 1277-1286.
35. Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983,** *48,* 2449-2452.
36. Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991,** *56,* 741-750.

(*Received in UK* 24 *July* 1995; *revised* 30 *August* 1995; *accepted* 1 *September* 1995)