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Microbial Reduction of 1-Tetralone 2-Carboxyesters as a Source of New Asymmetric Synthons

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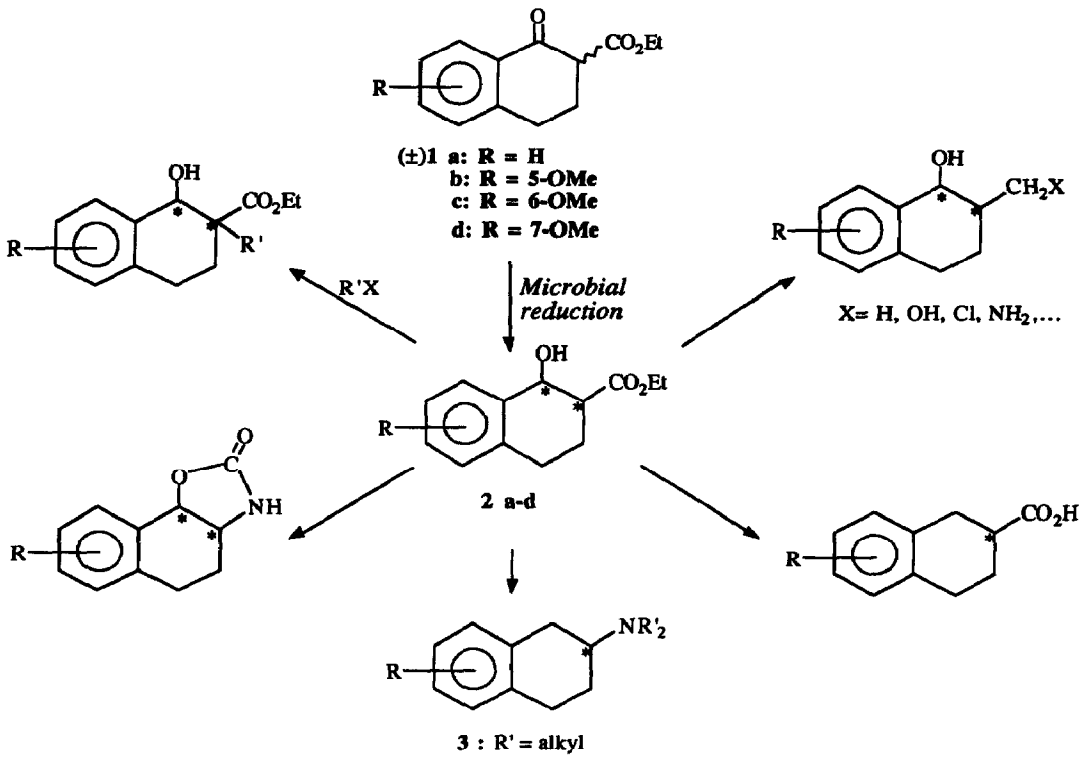
Abstract: The reduction of unsubstituted or methoxy-substituted (±)-2-carboxyethyl-1-tetralones by selected microorganisms affords optically active 1-hydroxy-2-carboxyethyl tetralins which can be used as versatile asymmetric synthons, for example in the preparation of biologically active methoxy-substituted 2R-aminotetralins. 1R,2R-(*cis*)-hydroxyesters of high optical purity are obtained with yeast strains, while the use of filamentous fungi leads to the enantiomeric 1S,2S-(*cis*)-hydroxyesters.

The reduction of (±)-α-substituted β-ketoesters by baker's yeast or other microorganisms is now a well established method[1-3] for the high yield, diastereoselective and enantiospecific preparation of α-substituted β-hydroxyesters having two asymmetric centers, resulting from a combination of the fast spontaneous epimerization of the substrate in the incubation medium and the stereospecific reduction of a single enantiomer [4-6]. This type of reaction, mainly utilizing baker's yeast, has been explored and shown to give practical results with a series of variously α-substituted β-ketoester substrates, such as α-methyl [4,6-12], α-alkyl- [13-15], α-hydroxy [16], α-sulfenyl [17,18], α-chloro [19,20], α-amino-β-keto-alkanoates [21], and various cyclic β-ketoesters derived from cycloalkanones [4,5,13,17,22-24]. A parallel chemical method, using catalytic hydrogenation in the presence of an asymmetric BINAP-Ru (II) complex, has been recently and concurrently developped [25].

However, only very few data have been reported till now about the microbial reduction of 1-oxo-1,2,3,4-tetrahydro-2-naphthalene carboxyesters **1**: using baker's yeast, the yields obtained with **1a** as substrate were low [23], although high diastereoselectivity and enantioselectivity were observed. Hydroxyesters **2**, or the corresponding hydroxyacids, obtained in a pure form as any one of the four possible stereomers, may constitute highly appreciated chiral synthons for the preparation, by simple reactions, of a number of very useful asymmetric molecules (Scheme 1). The unsubstituted members (**2a**) of this series have been previously prepared by separation of diastereomers and resolution of enantiomeric hydroxyacids [26]; they have been subsequently used for the conversion to optically active 2-methyl-tetralols and 2-aminotetralin. This approach thus offers a potential route for the synthesis of various related methoxy-substituted optically active molecules **3b-d**. These conformationally constrained analogues of dopamine or serotonin possess impressive biological activities as neurotransmitter agonists or antagonists [27,28], and have been in the past essentially obtained by classical resolution methods.

We report here the use of various microorganisms, selected among a number of yeast or fungi strains which have been tested to achieve such reductions, and the stereochemical outcome of these reactions.



Scheme 1

Contrarily to baker's yeast, which is only able to reduce the 7-methoxy derivative **1d** noticeably (Table), another yeast (*Saccharomyces montanus*) reduced all four ketoesters **1a-1d**. Analysis of the crude reduction products indicated, in all cases, the presence of a single diastereomer, further identified (see later) as the (1R, 2R)-*cis*-hydroxyester. Interestingly, the reduction of the 7-methoxy derivative **1d** by another yeast strain, *Rhodotorula glutinis*, afforded a 1: 1 mixture of the *cis*- and *trans*-hydroxyesters, both with high optical activities.

On the other hand, using miscelleanous fungal strains (Table), only (1S,2S)-*cis* hydroxyesters **2a-d** were obtained, whatever the aromatic substitution position was. Again, very high optical activities were observed, for example with *Mucor racemosus*, *Rhizopus arrhizus* or *Sporotrichum exile*, which produced nearly exclusively one isomer. The diastereomer ratios were determined by GC on the crude reduction products [29], and the relative configurations were assigned by ^{1}H-NMR on the purified products [30]. Enantiomeric ratios were determined after derivatization with (S)-O-acetyl lactyl chloride and GC of the resulting diastereomeric esters [31].

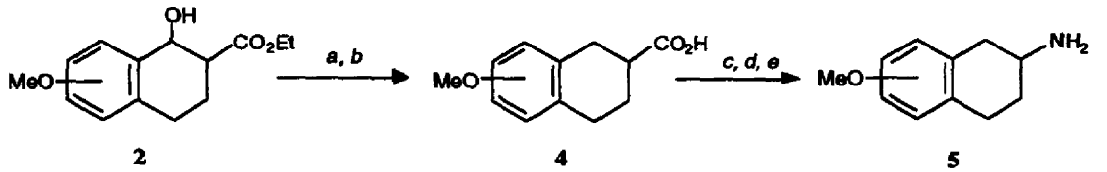
The absolute configurations of the hydroxyesters obtained by reduction of **1a** with *S.montanus* or *M.racemosus* were established by comparison of the sign of their optical rotations (See Table) with that described in the literature for the corresponding (1R,2R)-(+)-methyl ester [26]. For the reduction products of **1b**, obtained by using *S.montanus* or *S.exile*, it was first necessary to convert them (with retention of configuration) into the corresponding known enantiomeric (R)-(+)- or S-(–)-2-amino-5-methoxy-tetralins **5b** [32] by the reactions illustrated in Scheme 2. The reduction product of **1c**, obtained with *M.racemosus*, was similarly hydrogenated to 1,2,3,4-tetrahydro-6-methoxy-2-naphthalene carboxylic acid **4c**, converted to the corresponding 6-hydroxy methyl ester (HBr 48%, MeOH) then dehydroxylated [33] to the enantiomer of the

Table 1: Reduction of 2-carboxyethyl 1-tetralone **1a** and substituted derivatives **1b-d** by yeast or fungal strains (substrate concentration: 1g/litre; for other culture and incubation conditions, see [5]).

Substrate	Microorganism	Reduction time (hours)	Hydroxyester obtained			
			% [a]	*cis:trans* [b]	Configuration (e.e.%)[c]	$[\alpha]_D^{21}$ (EtOH)
1a	*Saccharomyces montanus* CBS 67-72	96	95	>99:1	1R,2R (98)	+115 (c 1.39)[e]
	Mucor racemosus [d]	72	83(48)	>99:1	1S,2S (99)	−116 (c 1.35)[e]
1b	*Saccharomyces montanus* CBS 67-72	68	97(71)	>99:1	1R,2R (93)	+111 (c 1)
	Mucor racemosus [d]	48	75	99:1	1S,2S (>99)	-
	Sporotrichum exile QM 1250	48	88 (51)	>99:1	1S,2S (99)	−115 (c 1.1)
	Rhizopus arrhizus ATCC 24563	72	60	>99:1	1S,2S (>99)	-
1c	*Saccharomyces montanus* CBS 67-72	168	74(25)	>99:1	1R,2R (90)	+100 (c 0.92)
	Mucor racemosus [d]	72	40(40)	>99:1	1S,2S (99)	−110 (c 0.72)
	Sporotrichum exile QM 1250	48	60	99:1	1S,2S (>99)	-
1d	Baker's yeast	72	70(32)	>99:1	1R,2R (95)	+71 (c 0.83)
	Rhodotorula glutinis NRRL Y-1091	48	55	1:1	1R,2R (90)[f]	-
	Saccharomyces montanus CBS 67-72	168	77	>99:1	1R,2R (49)	-
	Mucor racemosus [d]	48	70	99:1	1S,2S (>99)	-
	Rhizopus arrhizus ATCC 11145	72	79(52)	>99:1	1S,2S (>99)	− 72 (c 0.75)
	Rhizopus arrhizus ATCC 24563	72	98	>99:1	1S,2S (>99)	-
	Sporotrichum exile QM 1250	24	31	>99:1	1S,2S (>99)	-

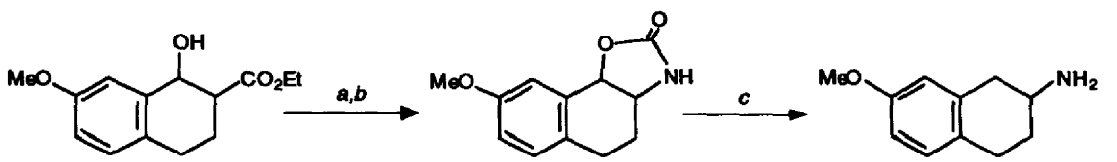
[a] % hydroxyester determined by GC in the crude extract (% isolated yield). [b] determined by GC. [c] determined by GC after derivatization as (S)-O-acetyllactyl esters. [d] local strain. [e] lit.[25] for the corresponding (1R,2R)-methyl ester: +121.7 (c 2, EtOH). [f] 99% e.e. for the *trans* isomer (absolute configuration not determined).

known (R)-(+)-1,2,3,4-tetrahydro-2-naphthalene carboxylic acid methyl ester [26]. The reduction product of **1d**, obtained with *R.arrhizus*, was hydrolyzed and hydrogenated into the corresponding 1,2,3,4-tetrahydro-7-methoxy-2-naphthalene carboxylic acid (S)-(−)-**4d** [34]. Using an alternative method, the same 7-methoxy-hydroxyester **1d** was converted in high yield into the known (S)-(−)-2-amino-7-methoxy-tetralin **5d** [35] (Scheme 3) through catalytic hydrogenation [36] of the oxazolidinone **6**, obtained by a modified Curtius rearrangement of the hydroxyacid using diphenylphosphoryl azide [37].



2 **4** **5**

Scheme 2
a : OH^-/water-EtOH; *b* : Pd/C (5%)/AcOH-$HClO_4$; *c* : $(COCl)_2/Et_2O$; *d* : NaN_3/Et_2O; *e* : H^+, 100°C



2d **6** **5d**

Scheme 3
a : OH^-/water-EtOH; *b* : DPPA, Et_3N/toluene, 110°C; *c*: Pd/C (10%)/HCl (5%) in EtOH.

It is remarkable that, while essentially *cis*-isomers are obtained, an opposite absolute configuration is systematically observed in the reduction products obtained from yeasts, compared to moulds. The chemical conversions of hydroxyesters, here described to demonstrate their absolute configurations, partly illustrate the versatility of these synthons, together with the preparation of asymmetric aminoalcohols [38] and bioactive amines [27,28,39] based on the 1,2,3,4-tetrahydronaphthalene skeleton.

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29. Flexibond™ OV-1701 capillary column (Pierce Chem. Co, 15m x 0.25 mm) operated at 170°C (ret.times: *cis*-**2a**, 13.54; *trans*-**2a**, 13.93 min), 190°C (*cis*-**2d**, 17.40; *trans*-**2d**, 18.02 min), or 200°C (*cis*-**2b**, 11.58; *trans*-**2b**, 11.81; *cis*-**2c**, 13.19 min).
30. *Cis* or *trans* relative configurations of the 1-hydroxyl and 2-carboxyethyl groups are easily recognized in this series by the respective values of the coupling constant of 1-C*H*OH (d, 4.85-5 ppm) with H-2: 3 Hz (corresponding to an *ax-eq* coupling) or 8.5 Hz (*ax-ax* coupling) [26].
31. Flexibond™ OV-1701 capillary column (Pierce Chem. Co, 15m x 0.25 mm) operated at 160-190°C (1°C/min; ret.times: 1S,2S-**2a**, 38.32; 1R,2R-**2a**, 38.69 min), 190°C (10 min) then 190-220°C (2°C/min; 1S,2S-**2b**, 31.36; 1R,2R-**2b**, 31.79 min), 200°C (10 min) then 200-210°C (3°C/min; 1S,2S-**2c**, 20,18; 1R,2R-**2c**, 20.46 min), or 200-230°C (3°C/min; 1S,2S-**2d**, 23.77; 1R,2R-**2d**, 24.12 min).
32. (S)-(–)-**5b**, HCl : $[a]_D^{21}$ – 61 (c 2.3, MeOH); lit.[40](see also[41]): $[a]_D^{20}$ – 61 (c 2, MeOH).
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