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Bioreduction of aromatic ketones: preparation of chiral benzyl alcohols in both enantiomeric forms

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Abstract

Substituted phenacyl chlorides are reduced with whole-cell biocatalysts to give (*R*)- or (*S*)-chlorohydrines in high yields and to make them good for high enantiomeric excess. Yields and enantiomeric purity of the *S*-enantiomer could be increased by performing bioreduction in the presence of polymeric absorbing resins. With this methodology, 2-chloro-1(*S*)-(3,4-dichloro-phenyl)-ethanol of 98% e.e. and 2-(*R*)-(4-nitro-phenyl)-ethanol of 92% e.e. have been prepared and used respectively as precursors in the synthesis of (+)-*cis*-1(*S*),4(*S*)-sertraline and of the β-blocker (*R*)-nifenalol®.

Keywords: Whole-cell biotransformations; Chloroacetophenone; Adsorbing resins; Sertraline; Nifenalol

1. Introduction

The asymmetric reduction of ketones is one of the more useful reactions for the introduction of chirality into a target molecule, an important process to obtain alcohols, which are valuable intermediate in the preparation of chiral drugs. In fact, in many cases, secondary alcohols are the key compound in their synthesis. To compete with synthetic methods, a biocatalytic process should be efficient, highly stereospecific and easy to perform.

The use of biocatalysts for the asymmetric reduction of ketones relies on the availability of a suitable enzyme or whole-cell biocatalyst. The latter form is usually preferred on an industrial scale in order to avoid the problem of cofactor regeneration [1]. However, a special catalyst must be developed for each substrate. There is a number of easy-to-grow GRAS (generally recognised as safe) microorganisms whose substrate specificity is rather broad [1]. Among them, a useful and efficient biocatalyst is often found. Even if the prevalent enantiopreference in the reduction gives alcohols with *R* absolute configuration, microorganisms giving alcohols belonging to the *S* family can be encountered [2]. Asymmetric reduction of aryl-α-halomethyl ketones is potentially a useful process to obtain halohydrins, intermediates in the preparation of a large group of α- and β-adrenergic drugs (Fig. 1).

Although many data are available for the reduction of aryl-α-halomethyl ketones [3a,b,c,d], very few examples are reported where the aromatic ke-

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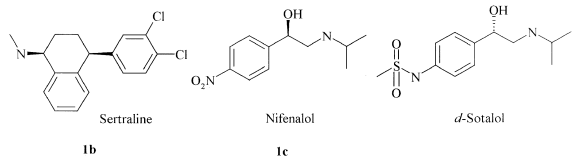


Fig. 1.

tone bears on the phenyl ring the suitable functional groups found in the target molecule [4a,b,5].

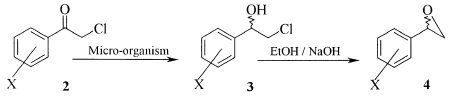
We report in this article the biocatalytic reduction of **2** to give the corresponding chloro-benzyl alcohols **3** in both absolute configurations converted in turn into the oxirane **4** useful synthon in the synthesis of chiral pharmaceuticals compounds (Scheme 1).

The alcohol **3b** of *S*-absolute configuration is then transformed into **5**, the intermediate in the synthesis of Sertraline **1b** [6]. The halohydrin **3c**, of *R* absolute configuration,was converted into the oxirane **4c** precursor of *R*-Nifenalol **1c** [7]. Parallel experiments have been conducted on α-chloro-acetophenone **2a** to confirm the stereochemical preference of the microorganisms and onto 3,4-dichloro-benzofenone **6** whose reduction with whole-cell biocatalyst has hardly been reported (Scheme 2).

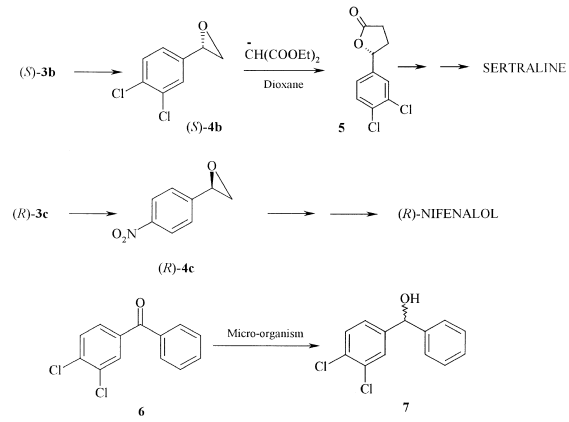
2. Materials and methods

2.1. Analytical

GC chiral analysis were performed on a DANI 8610 apparatus with a FID detector fitted with a glass capillary column. Megadex DetTBuSiβ-cdx (Mega, Legnano, Italy), 25 m × 0.25 mm i.d., film thickness 0.25 μm. $[\alpha]_D$ were recorded with a Propol automatic digital polarimeter. ^{1}H NMR were recorded on a Varian EMX 300 MHz with TMS as internal



Scheme 1.



Scheme 2.

standard, all spectra were recorded in $CDCl_3$ unless otherwise indicated.

2.2. General conditions for microbes culture

All the microorganisms tested, except *R. mucillaginosa*, *P. subpelliculosa* and *Y. lipolytica*, were grown in a plate of solid MPGA medium (D-glucose 20 g/l, peptone 5 g/l, malt 20 g/l, agar 15 g/l) for 48 h at 28°C. Fifty milliliters of MPGB medium (D-glucose 20 g/l, peptone 5 g/l, malt 20 g/l) in a 300-ml Erlenmeyer flask was inoculated with the microorganism and the flask shaken at 120 rpm for 24 h at 28°C. Five milliliters of the content of the flask were transferred in 50 ml of fresh MPGB medium and shaken for an additional 24 h in the same conditions. At this point, the microrganism is ready for the addition of substrate, either dissolved in EtOH or adsorbed onto the resin. The medium used for *R. mucillaginosa*, *P. subpelliculosa* and *Y. lipolytica* was GPYA (D-glucose 40 g/l, peptone 5 g/l, yeast extract 5 g/l, agar 15 g/l) for the plates and GPY (D-glucose 40 g/l, peptone 5 g/l, yeast extract 5 g/l) for the flasks.

2.3. Adsorption of the substrates onto the resin

The crude commercial resin (XAD1180, XAD7 and S112) was washed subsequently with deionised water and acetone (3 ml for 1 ml of resin) and dried at reduced pressure. The substrate was dissolved in

acetone and the resin, added to the solution (i.e. 1 g of substrate, 10 ml of acetone and 2 g of dry resin). The mixture was shaken for 10 min and then the acetone was evaporated at reduced pressure. The solid obtained was poured directly into the fermentation flask.

2.4. 2-Chloro-1-(3,4-dichloro-phenyl)-ethanone **2b**

It was prepared as reported in literature [8]: 1,2-dichloro-benzene, chloro-acetylchloride, $AlCl_3$, CS_2, 50°C, 24 h. Anal calcd for $C_8H_5Cl_3O$: C, 43.00; H, 2.26; Cl, 47.59. Found: C, 43.08; H, 2.31; Cl, 47.52.

2.5. 2-Chloro-1-(4-nitro-phenyl)-ethanone **2c**

It was prepared as reported in the literature [9]: *p*-NO_2-acetophenone, $CHCl_3$, SO_2Cl_2, 50°C, 5 h. Anal calcd for $C_8H_6ClNO_3$: C, 48.14; H, 3.03; Cl, 17.76; N, 7.02. Found: C, 48.10; H, 3.01; Cl, 17.69; N, 7.00.

2.6. (3,4-Dichloro-phenyl)-phenyl-methanone **6**

It was prepared as reported in the literature [10]: 3,4-dichloro-benzoyl-cholride, benzene, $AlCl_3$, reflux 5 h. Anal calcd for $C_{13}H_8Cl_2O$: C, 62.18; H, 3.21; Cl, 28.24. Found: C, 62.08; H, 2.30; Cl, 28.22.

2.7. General fermentation conditions

2.7.1. Fermentation in normal conditions

To a culture of the microorganism (see Table 1), 50 ml, grown as described above, 50 mg of substrate (**2a**, **2b**, **2c** or **6**, respectively) were added, dissolved

Table 1
Bioreduction of **2a**, **2b**, **2c** and **6** at 1 g/l initial concentration

Microorganism	Product											
	3a			3b			3c			**7**		
	(i)	(ii)	(iii)	(i)	(ii)	(iii)	(i)	(ii)	(iii)	(i)	(ii)	(iii)
P. menbranaef. CBS107	0			0		[a]	0		0			
D. hansenii. CBS116	0			11	[a]		0			0		
Z. rouxii ATCC2623	0			0			0			0		
B. bassiana ATCC7159	58	82	*S*	41	87	*S*	70	92	*S*	0		
M. subtilissimus	99	96	*R*	78	82	*R*	99	91	*R*	0		
P. chrysosporium	41	[a]	[a]	0			0			0		
A. niger IPV283	90	78	*S*	50	89	*S*	29	[a]	[a]	0		
C. lunata CBS215.54	25	[a]	[a]	0			0			0		
G. candidum CBS233.76	99	85	*S*	95	93	*S*	99	97	*S*	0		
Baker's yeast[b]	95	41	*R*	99	41	*R*	12	[a]	[a]	0		
R. glutinis CBS20	15	[a]	[a]	11	[a]	[a]	13	[a]	[a]	0		
Y. lipolytica CBS6317	87	71	*S*	85	92	*S*	99	95	*S*	3	[a]	[a]
R. mucillagin. CBS2378	60	98	*R*	88	99	*R*	49	92	*R*	28[c]	53[d]	[a]
P. subpellicul. CBS5767	32	[a]	[a]	26	[a]	[a]	6	[a]	[a]	0		
F. caucasic. CBS580.78	70	53	*S*	61	[a]	[a]	99	97	*S*	0		
A. niveus CBS114.33	40	[a]	[a]	66	[a]	[a]	47	[a]	[a]	1		
C. lypolytica CBS2074	24	[a]	[a]	13	[a]	[a]	12	[a]	[a]	0		
P. ohmeri CBS5367	19	[a]	[a]	14	[a]	[a]	8	[a]	[a]	0		
K. saturnus CBS5761	0			0			0			0		
H. anomala CBS110	0			0			0			0		
P. stipitis CBS5773	15	[a]	[a]				14	[a]	[a]	0		
P. pastoris CBS704	31	[a]	[a]	10	[a]	[a]	17	[a]	[a]	0		

(i) Conversion. (ii) Enantiomeric excess. (iii) Absolute configuration.
[a] Non-determined.
[b] Distillerie Italiane, Eridania Group.
[c] After 168 h of biotransformation.
[d] Chiral GC evidence by comparison with racemic **7** obtained from $NaBH_4$ reduction of **6**.

in 1 ml of absolute EtOH. The culture was left for 48 h at 28°C on a linear shaker at 120 rpm. To the crude fermentation medium, 50 ml of ethyl acetate were added, the mixture was filtered over a Celite pad and the biomass was washed with ethyl acetate (2×10 ml). The organic solvent, once dried over Na_2SO_4 and evaporated under reduced pressure, left a brown oil, which was used directly for the GC analysis. Bulb to bulb distillation gave access, in this way, to pure (*R*) and (*S*) **3a**, **3b** and **3c**. Product **7** was not purified.

The physical properties reported below for **3a**, **3b** and **3c** are in good agreement with the data reported in the literature. (*S*)-**3a** 91% yield, $[\alpha]_D = +40.9$ (c1.8, cyclohexane), e.e. 85% (*G. candidum*); (*R*)-**3a** yield 91%, $[\alpha]_D = -46.2$ (c1.8, cyclohexane) (lit [11] −48.1), e.e. 96% (*M. subtilissimus*); ^{1}H NMR δ 2.60 (1H, OH, s), 3.70 (2H, CH_2, m), 4.87 (1H, CH, dd) and 7.37 (5H, Ph, m). Anal calcd for C_8H_9ClO: C, 61.35; H, 5.79; Cl, 22.64. Found: C, 61.68; H, 5.71; Cl, 22.62. (*S*)-**3b** yield 83%, $[\alpha]_D = +31$ (c1, $CHCl_3$), e.e. 93% (*G. candidum*); (*R*)-**3b**, yield 80%, $[\alpha]_D = -32.7$ (c1, $CHCl_3$), e.e. 99% (*R. mucillaginosa*); ^{1}H NMR δ 1.87 (1H, OH, broad), 3.59 (1H, CH_2, dd), 3.72 (1H, CH_2, dd), 4.86 (1H, CH, dd) and 7.20–7.52 (3H, Ph, m). Anal calcd for $C_8H_7Cl_3O$: C, 42.61; H, 3.13; Cl, 47.17. Found: C, 42.65; H, 3.11; Cl, 47.19. (*S*)-**3c** yield 82%, $[\alpha]_D = +36.9$ (c1, $CHCl_3$), e.e. 97% (*G. candidum*); (lit [12] +37.2); (*R*)-**3c**, yield 80%, $[\alpha]_D = -34.8$ (c1, $CHCl_3$), e.e. 91% (*M. subtilissimus*); ^{1}H NMR δ 2.58 (1H, OH, broad), 3.64 (1H, CH_2, dd), 3.78 (1H, CH_2, dd), 5.03 (1H, CH, dd), 7.61 (2H, Ph, d) and 8.26 (2H, Ph, d). Anal calcd for $C_8H_8ClNO_3$: C, 47.66; H, 4.00; Cl, 17.59; N, 6.95. Found: C, 47.68; H, 4.01; Cl, 17.52; N, 7.01.

2.7.2. Fermentation in the presence of absorbing resins

In the case of the use of absorbing resins, 100 mg of the substrate, (**2b** or **2c**, respectively), absorbed onto 200 mg of the resin, were directly poured into 50 ml of the culture of the microorganism. The culture was left for 48 h at 28°C on a linear shaker at 120 rpm. Product recovery was performed by filtering the crude mixture through a sintered glass funnel (pore size 0) and extracting the resin with 3×10 ml of ethyl acetate. The organic solvent, once dried over Na_2SO_4 and evaporated under reduced pressure, left a brown oil, which was used directly for the GC analysis. Bulb to bulb distillation gave access, in this way, to pure (*R*) and (*S*) **3b** and **3c**. (*S*)-**3b** yield 91%, $[\alpha]_D = +32.5$ (c1, $CHCl_3$), e.e. 98% (*G. candidum*, XAD1180); (*R*)-**3b**, yield 89%, $[\alpha]_D = -24$ (c1, $CHCl_3$), e.e. 73% (*R. mucillaginosa*, S112); (*S*)-**3c** yield 90%, $[\alpha]_D = +36.9$ (c1, $CHCl_3$), e.e. 97% (*G. candidum*, S112); (*R*)-**3c**, yield 95%, $[\alpha]_D = -37.8$ (c1, $CHCl_3$), e.e. 99% (*R. mucillaginosa*, XAD7).

2.8. (3,4-Dichloro-phenyl)-phenyl-methanol 7

6 was reduced by $NaBH_4$ in EtOH in the usual way so as to obtain after purification by flash chromatography pure **7**, yield 85%, ^{1}H NMR δ 2.18 (1H, OH, broad), 5.76 (1H, CH, s) and 7.10–7.57 (8H, Ph, m). Anal calcd for $C_{13}H_{10}Cl_2O$: C, 61.69; H, 3.98; Cl, 28.01. Found: C, 61.68; H, 4.01; Cl, 27.92.

2.9. Oxirane 4a, 4b, and 4c

Literature procedure [13] was followed for the preparation of the oxirane **4**. (*S*)-**4a** 87% yield, $[\alpha]_D = -4.8$ (c2.5, acetone), e.e. 85%; (*R*)-**4a**, 86% yield, $[\alpha]_D = +5.5$ (c2.5, acetone), e.e. 96% (lit [14], +6.7). (*S*)-**4b** 90% yield, $[\alpha]_D = +14.3$ (c1, $CHCl_3$), e.e. 93%; (*R*)-**4b** 88% yield, $[\alpha]_D = -15.7$ (c1, $CHCl_3$), e.e. 99%; ^{1}H NMR δ 2.72 (1H, CH_2, dd), 3.14 (1H, CH_2, dd), 3.81 (1H, CH, dd), 7.11 (1H, Ph, m) and 7.48 (2H, Ph, m). Anal calcd for $C_8H_6Cl_2O$: C, 50.83; H, 3.20; Cl, 37.51. Found: C, 50.88; H, 3.21; Cl, 37.52. (*S*)-**4c**, 90% yield, $[\alpha]_D = +37.2$ (c1, $CHCl_3$), e.e.98.8%; (*R*)-**4c**, 90% yield, $[\alpha]_D = -34.7$ (c1, $CHCl_3$), e.e.91%; ^{1}H NMR δ 2.78 (1H, CH_2, dd), 3.23 (1H, CH_2, dd), 3.96 (1H, CH, q), 7.44 (2H, Ph, d) and 8.22 (2H, Ph, d).Anal calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.25; H, 4.21; N, 8.52.

3. Results and discussion

α-Chloro-acetophenones **2a**, **2b** and **2c** and (3,4-dichloro-phenyl)-phenyl-methanone **6** were assayed

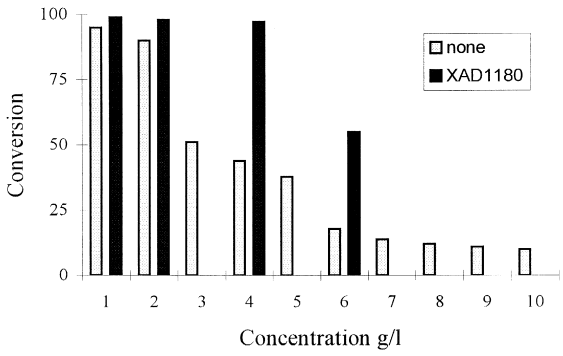


Fig. 2. Effect of initial concentration on the bioconversion of **2b** with *G.candidum*.

as substrates for a series of microorganisms from our collection (Table 1), which are known for their high reducing capacity. Assays were performed as reported in the experimental part. GC of an organic extract monitored the extent of conversion, while GC on chiral stationary phase determined the enantiomeric excess of the product. Absolute configurations have been determined by comparison of the specific rotations with the data known from the literature.

Several microorganisms were identified to give as a product the chlorohydrine with the *R* absolute configuration for all the substrates tested. Baker's yeast for instance gives **3a** in 95% conversion but only 41% e.e. The same compound can be obtained in 99% conversion and $>96\%$ e.e. with growing cultures of *M. subtilissimus*, which is also the microorganism of choice to obtain **3c** in high yield and good enantiomeric excess (91%). *R. mucillaginosa* is the microorganism that gives the best results with **3b** (90% conversion and 99% e.e.), and, also, the only microorganism found that is capable of reducing **6**, even at low conversion and poor e.e. (168 h, absolute configuration not assigned).

The *S* enantiomer of **3a**, **3b** and **3c** could be obtained with *G. candidum*, *Y. lipolytica* and *A. niger*. *G. candidum* gives the best results with all three substrates giving 85%, 93% and 97% e.e., respectively. Identical result is obtained with *F. caucasicum*, but only with substrate **2c**.

Compound **3b** with the absolute configuration required for the conversion outlined in Scheme 2 was converted into **5** as previously reported [13] while **3c**, of (*R*) absolute configuration, is converted by base treatment into **4c**, the oxirane precursor of (*R*)-nifenalol **1c** [7]. We noticed that if **3c** is not well purified (flash chromatography plus crystallisation), some racemization could take place during epoxidation).

At higher substrate concentration (>2 g/l), the conversion was considerably lower indicating the presence of substrate/product inhibition. In order to compete with asymmetric methods employing hydrogenation catalysts, space–time yields of the transformation is crucial. We have recently shown the beneficial effect of the presence of hydrophobic adsorbing resins in the selectivity and efficiency of whole-cell biotransformations [15–17]. The addition of adsorbing resins during the biotransformation lowers the actual concentration in the cells surrounding improving selectivity and product isolation. The presence of Amberlite XAD-1180 at 2:1 weight to weight ratio with **2b** allows the obtainement of compound **3b** in 95% yield and with an enantiomeric excess higher than 98% at concentrations of 4 g/l (Fig. 2).

In this way, compound **3b** was isolated in g amount [13]. Three different types of absorbing resins were tested with substrate **2b** and **2c** (see Table 2), XAD1180 and S112, which are polystirenic adsor-

Table 2
Comparison of the conversion and enantiomeric excess of product **3b** and **3c** obtained in the bioreduction of **2b** and **2c** in the presence of absorbing resins at 2 g/l initial concentration

Microorganism	Product							
	XAD1180		XAD7		S112		None	
	i	ii	i	ii	i	ii	i	ii
3b								
M. subtilissimus	82	66	90	32	83	18	45	82
G. candidum	98	98	82	98	85	98	90	92
R. mucillaginosa	98	76	98	78	95	73	85	99
3c								
M. subtilissimus	70	89	99	93	83	87	95	90
G. candidum	99	89	97	91	97	97	93	95
R. mucillaginosa	66	99	99	99	66	99	38	90

(i) Conversion. (ii) Enantiomeric excess. Absolute configuration as reported in Table 1.

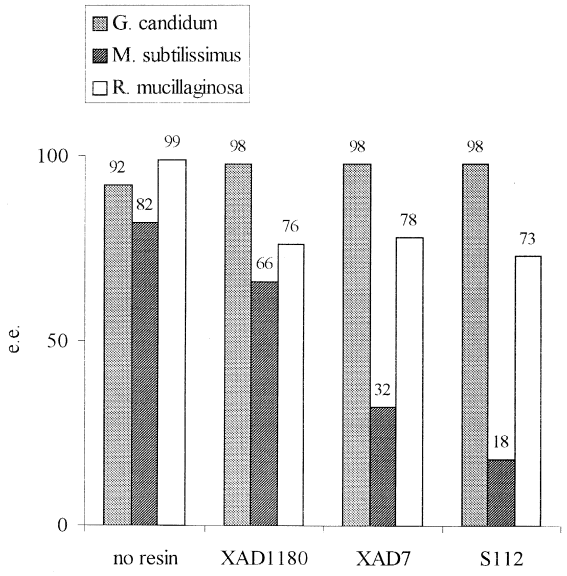


Fig. 3. Effect of absorbing resin on the biotransformation of **2b** in culture of *G. candidum*, *M. subtilissimus* and *R. mucillaginosa* at 2 g/l initial concentration.

bents and XAD7, a polyacrilic resin. The experiments were conducted with the microorganisms, which gave the best results in terms of conversion and enantiomeric excess. While the addition of the resin to the culture medium of *G. candidum* with substrate **2b** slightly increase the enantiomeric excess and allowed to double the initial concentration, a decrease in the e.e. took place with *R. mucillaginosa* and more evident with *M. subtilissimus*. The results are summarised in Fig. 3.

Interestingly enough, the addition of S112 absorbing resin in the bioreduction of **2b** with *M. subtilissimus* giving the *R* enantiomer of **3b** lowers the e.e. until 18%. This data is also confirmed by experiment conducted with a lower initial concentration of **2b** in the absence of absorbing resin (0.2 g/l, e.e. 64%). This means that, of the two enzymes competing for the enantioselective reduction, the *S*-enzyme is much more favoured by a lower initial concentration than the *R*-enzyme. A different behaviour was observed with substrate **2c** in the presence of absorbing resins and growing culture of *M. subtilissimus*, *G. candidum* and *R. mucillaginosa*. While it was still possible to double the initial concentration of substrate still maintaining a good conversion (> 90%), only a slight improvement in the enantiomeric excess was observed. Only in the case of *R. mucillaginosa* was a marked improvement in the e.e. observed in the preparation of **3c**, which was obtained in enantiomerically pure form (Table 2).

All the three resins have high absorbing capacity and the release into the medium of both, substrates and products, did not exceed 10% of the total. Only trace amounts of metabolites are recovered from extraction of the resins.

The results reported in this article show the versatility of whole-cell biocatalysts in the preparation of enantiopure secondary alcohols, in both enantiomeric forms. The products are eventually converted into the single enantiomers of chiral drugs

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