Research Article

Chiral Pharmaceutical Intermediaries Obtained by Reduction of 2-Halo-1-(4-substituted phenyl)-ethanones Mediated by Geotrichum candidum CCT 1205 and Rhodotorula glutinis CCT 2182

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Received 14 January 2011; Accepted 10 March 2011

Academic Editor: Robert F. H. Dekker

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Enantioselective reductions of $p$-R$_1$-C$_6$H$_4$(O)CH$_2$R$_2$ (R$_1$ = Cl, Br, CH$_3$, OCH$_3$, NO$_2$ and R$_2$ = Br, Cl) mediated by Geotrichum candidum CCT 1205 and Rhodotorula glutinis CCT 2182 afforded the corresponding halohydrins with complementary $R$ and $S$ configurations, respectively, in excellent yield and enantiomeric excesses. The obtained ($R$)- or ($S$)-halohydrins are important building blocks in chemical and pharmaceutical industries.

1. Introduction

Chiral halohydrins are important and valuable intermediates in the synthesis of fine chemicals and pharmaceuticals as optically active 1,2-aminoalcohols. The halohydrin ($R$)-1-aryl-2-haloethanol may be used for the preparation of ($R$)-1-aryl-2-aminoethanols that are used as $\alpha$- and $\beta$-adrenergic drugs.

An interesting chemoenzymatic synthetic route to obtain optically active 1-aryl-2-ethanolamines is from the enantioselective reduction of the correspondent $\alpha$-haloacetophenones giving halohydrins that are transformed into an epoxy that reacts with the appropriate amine (Scheme 1) [1, 2].

An enormous potential of the use of microorganisms and enzymes for the transformation of synthetic chemicals with high chemo-, regio-, and enantioselectivity has been increasing in the pharmaceutical industry [3]. The dehydrogenases in the form of whole cells for the production of chiral styrene oxides have been used on a pilot-plant scale [4]. Therefore, a large number of papers have appeared reporting the enantiomeric reduction of $\alpha$-bromoacetophenone [5-10] and $\alpha$-chloroacetophenone [4, 6, 7, 11-17] by whole cells of microorganism and also by isolated enzyme [18] giving halohydrins in high enantiomeric excesses (ee).

There are few examples of biocatalytic reduction of $\alpha$-haloacetophenone having suitable substituted group attached to the aromatic ring for enantioselective preparation of some target 1-aryl-2-ethanolamines [2, 19]. It is known that some examples of biocatalytic reductions of $\alpha$-haloacetophenone that have substituted groups like 3-chloro [20, 21], 4-nitro [10, 22], and 3,4-methylenedioxy [23-25] were mediated by a number of microorganisms. Also, isolated enzymes have been used to reduce $\alpha$-haloacetophenone having various kinds of substituted groups [26, 27].

The performances of Rhodotorula glutinis CCT 2182 and Geotrichum candidum CCT 1205 in bioreduction of $\alpha$-haloacetophenone have been calling our attention due to the efficiency and complementary enantioselectivity of these microorganisms giving the corresponding ($R$)- and ($S$)-halohydrins in high ee, respectively [8]. Also, those microorganisms show the same efficiency in the reduction of $\alpha$-azido-para-substituted acetophenones [28]. In this work, we use those two microorganisms for reduction of $\alpha$-bromo- and $\alpha$-chloroacetophenones having para-substituted groups to produce separately both enantiomers of halohydrins that can be used as chiral building blocks for preparations of the corresponding 1,2-aminoalcohols.
2. Materials and Methods

IR spectra were recorded on a Bomem MB Series spectrometer. 1H and 13C NMR spectra were recorded on a Varian Gemini 300 spectrometer in CDCl3. Gas chromatographic analyses were performed using a Shimadzu GC/MS Class 5000, with helium as carrier gas. The fused silica capillary columns used were either a Supelco Simplicity ITM (30 m × 0.25 mm × 0.25 μm) and a chiral GC-column CHIRASILDEX (30 m × 0.25 mm × 0.25 μm). Optical rotation was measured with a J-720, VRDM306 JASCO, 589.3 nm (200 rpm) at 28°C for G. candidum and at 30°C for R. glutinis until the full conversion of 1 (18 h). The product was extracted with CH2Cl2 and purified by flash silica gel column chromatography using hexane/ethyl acetate (7:3).

The yeasts were incubated for two days (400 mL nutrient broth in Erlenmeyer of 1 L). After that, the ketone 1 (2 mmol) dissolved in 1.5 mL of ethanol was added directly to the suspension where the yeasts grew. The resulting suspension was stirred in an orbital shaker (200 rpm) at 28°C for G. candidum and at 30°C for R. glutinis until the full conversion of 1 (18 h). The product was extracted with CH2Cl2 and purified by flash silica gel column chromatography using hexane/ethyl acetate (7:3).

2.2. General Procedure for Bioreduction of 2-Halo-1-(4-substituted phenyl)-ethanones. The yeasts were incubated for two days (400 mL nutrient broth in Erlenmeyer of 1 L). After 25°C for 18 h. The product was extracted with CH2Cl2 and purified by flash silica gel column chromatography using hexane/ethyl acetate (7:3).
(300 MHz, CDCl₃) δ 2.74 (s, 1H, OH), 3.48 (dd, 1H, J = 7.0 Hz and 11.3 Hz, CH₂), 3.61 (dd, 1H, J = 5.8 Hz and 7.0 Hz, CH), 7.24–7.28 (m, 2H, Ph), 7.31–7.35 (m, 2H, Ph); ¹³C NMR (75 MHz, CDCl₃) δ 39.72, 72.97, 122.12, 127.43, 131.56, 139.00; MS m/z (rel. int. %): 143 (29), 142 (11), 141 (100), 139 (4), 138 (2), 121 (7), 115 (6), 113 (16), 112 (6), 111 (4), 108 (7), 107 (5), 105 (4), 104 (2), 102 (2), 91 (2), 89 (1), 79 (11), 78 (9), 77 (70), 76 (2), 75 (15), 74 (9), 70 (6), 63 (8), 51 (28), 50 (30), 49 (3), 44 (22), 43 (20), 40 (32).

2.6. (R)-(−)-2-Bromo-1-(4-chlorophenyl)ethanol (R)-2b. The bioreduction of ketone 1b (0.467 g, 2 mmol) by Rhodotorula glutinis CCT 2182 furnished (R)-2b (0.457 g, 97.0% yield) as colorless oil; [α]D 42.12° = −38.7 (c 1, CHCl₃) [lit. 38.6, c 1.15, CHCl₃ for S isomer, 91% ee] [32], giving an optical purity of >99% determined by GC using a chiral column; ¹H and ¹³C NMR and IR spectra and MS analysis were identical to those observed with its (S) enantiomer.

2.7. (S)-(−)-2-Bromo-1-(4-methylphenyl)ethanol (S)-2c. The bioreduction of ketone 1c (0.426 g, 2 mmol) by Geotrichum candidum CCT 1205 furnished (S)-2c (0.413 g, 96.0% yield) as colorless oil; [α]D 42° = +48.3° (c 1, CHCl₃) [lit. +41.8°, c 1, CHCl₃ for S isomer, 95% ee] [32], giving an optical purity of >99% determined by GC using a chiral column; IR (film): 3378, 3062, 2973, 2928, 2907, 2878, 1616, 1581, 1511, 1458, 1442, 1368, 1300, 1240, 1205, 117, 112, 108, 102, 991, 830, 804 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.72 (s, 1H, OH), 3.61 (dd, 1H, J = 8.7 Hz and 11.2 Hz, CH₂), 3.70 (dd, 1H, J = 3.9 Hz and 11.2 Hz, CH₂), 3.79 (s, 3H, CH₃), 4.86 (dd, 1H, J = 3.9 Hz and 8.7 Hz, CH), 6.89 (d, 2H, J = 8.8 Hz, Ph), 7.31 (d, 2H, J = 8.8 Hz, Ph); ¹³C NMR (75 MHz, CDCl₃) δ 42.12, 56.28, 72.98, 114.94, 127.71, 133.40, 160.03; MS m/z (rel. int. %): 233–231 (M⁺, 1), 218 (1), 215 (1), 214 (1), 202 (2), 200 (2), 153 (2), 152 (4), 151 (2), 138 (6), 137 (100), 135 (11), 134 (9), 122 (2), 121 (2), 120 (2), 119 (20), 110 (3), 109 (16), 108 (3), 107 (2), 105 (2), 104 (1) 103 (4), 102 (2), 95 (3), 94 (16), 93 (2), 92 (7), 91 (18), 90 (2), 89 (4), 81 (2), 79 (6), 78 (5), 77 (21), 76 (2), 75 (3), 68 (2), 67 (2), 66 (5), 65 (12), 64 (9), 63 (6), 55 (1), 54 (1), 53 (8), 52 (4), 51 (12), 50 (14), 45 (3), 44 (2), 43 (79), 41 (10), 40 (8).

2.10. (R)-(−)-2-Bromo-1-(4-methylphenyl)ethanol (R)-2d. The bioreduction of ketone 1d (0.458 g, 2 mmol) by Rhodotorula glutinis CCT 2182 gave (R)-2d (0.452 g, 97.8% yield) as colorless oil; [α]D 41.8° = −19.7° (c 1, CHCl₃) [lit. −37.7°, c 1.0, CHCl₃ for R isomer, 87% ee] [31], ¹H and ¹³C NMR and IR spectra and MS analysis were identical to those observed with its (S) enantiomer.

2.11. (S)-(−)-2-Bromo-1-(4-nitrophenyl)ethanol (S)-2e. The bioreduction of ketone 1e (0.488 g, 2 mmol) by Geotrichum candidum CCT 1205 gave (S)-2e (0.480 g, 97.6% yield) a light yellow solid, mp 98°C; [α]D 42° = +25.0° (c 1, CHCl₃) [lit. +32.1°, c 1, CHCl₃ for S isomer, 91% ee] [33], giving an optical purity of >99% determined by GC using a chiral column; IR (KBr): 3455, 3109, 2947, 2924, 2889, 2851, 1601, 1520, 1347, 1291, 1203, 1074, 1012, 855, 760, 730 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.83 (s, 1H, OH), 3.53 (dd, 1H, J = 8.4 Hz and 10.6 Hz, CH₂), 3.68 (dd, 1H, J = 3.5 Hz and 10.6 Hz, CH₂), 5.03–5.08 (m, 1H, CH₂), 7.45 (d, 2H, J = 8.8 Hz, Ph), 8.22 (d, 2H, J = 8.8 Hz, Ph); ¹³C NMR (75 MHz, CDCl₃): δ 39.32, 72.52, 123.60, 126.65, 146.10, 146.90; MS m/z (rel. int. %): 153 (8), 152 (100), 149 (2), 141 (1), 139 (1), 136 (2), 127 (1), 125 (2), 122 (5), 106 (10), 105 (9), 102 (4), 95 (5), 94 (11), 91 (8), 78 (13), 77 (17), 76 (6), 51 (17), 50 (13), 43 (20).

2.12. (R)-(−)-2-Bromo-1-(4-nitrophenyl)ethanol (R)-2f. The bioreduction of ketone 1f (0.467 g, 2 mmol) by Rhodotorula glutinis CCT 2182 gave (R)-2f (0.483 g, 98.0% yield) a light yellow solid, mp 98°C; [α]D 42° = −25.0° (c 1, CHCl₃) [lit. +32.1°, c 1, CHCl₃ for S isomer, 91% ee] [33, 36], giving an optical purity of >99% determined by GC using a chiral column; ¹H and ¹³C NMR and IR spectra and MS analysis were identical to those observed with its (S) enantiomer.

2.13. (S)-(−)-2-Chloro-1-(4-bromophenyl)ethanol (S)-2f. The bioreduction of ketone 1f (0.467 g, 2 mmol) by Geotrichum candidum CCT 1205 gave (S)-2f (0.468 g, 99.4% yield) as colorless oil; [α]D 42° = +35.0° (c 1, CHCl₃) [lit. −35.87°, c 1.1072, CHCl₃ for R isomer, 99% ee] [14], giving an optical purity of >99% determined by GC using a chiral column; IR (film):
The bioreduction of ketone 1f (0.467 g, 2 mmol) by *Rhodotorula glutinis* CCT 2182 gave (R)-2f (0.460 g, 97.7% yield) as colorless oil; m/z 25: 3.7 (1), 3.6 (2), 3.5 (1), 3.4 (100), 3.3 (1), 3.2 (1), 3.1 (9), 3.0 (1), 2.9 (1), 2.8 (1), 2.7 (1), 2.6 (1), 2.5 (1), 2.4 (1), 2.3 (1), 2.2 (1), 2.1 (2), 2.0 (1), 1.9 (1), 1.8 (1), 1.7 (1), 1.6 (1), 1.5 (1), 1.4 (1), 1.3 (1), 1.2 (1), 1.1 (1), 1.0 (1), 0.9 (1), 0.8 (1), 0.7 (1), 0.6 (1), 0.5 (1), 0.4 (1), 0.3 (1), 0.2 (1), 0.1 (1), 0.0 (1).

The bioreduction of ketone 1g (0.378 g, 2 mmol) by *Geotrichum candidum* CCT 1205 furnished (S)-2g (0.363 g, 95.0% yield) as colorless oil; m/z 25: 3.7 (1), 3.6 (2), 3.5 (1), 3.4 (100), 3.3 (1), 3.2 (1), 3.1 (9), 3.0 (1), 2.9 (1), 2.8 (1), 2.7 (1), 2.6 (1), 2.5 (1), 2.4 (1), 2.3 (1), 2.2 (1), 2.1 (2), 2.0 (1), 1.9 (1), 1.8 (1), 1.7 (1), 1.6 (1), 1.5 (1), 1.4 (1), 1.3 (1), 1.2 (1), 1.1 (1), 1.0 (1), 0.9 (1), 0.8 (1), 0.7 (1), 0.6 (1), 0.5 (1), 0.4 (1), 0.3 (1), 0.2 (1), 0.1 (1), 0.0 (1).

The bioreduction of ketone 1h (0.369 g, 2 mmol) by *Rhodotorula glutinis* CCT 1205 furnished (S)-2i (0.370 g, 99.2% yield) as colorless oil; m/z 25: 3.7 (1), 3.6 (2), 3.5 (1), 3.4 (100), 3.3 (1), 3.2 (1), 3.1 (9), 3.0 (1), 2.9 (1), 2.8 (1), 2.7 (1), 2.6 (1), 2.5 (1), 2.4 (1), 2.3 (1), 2.2 (1), 2.1 (2), 2.0 (1), 1.9 (1), 1.8 (1), 1.7 (1), 1.6 (1), 1.5 (1), 1.4 (1), 1.3 (1), 1.2 (1), 1.1 (1), 1.0 (1), 0.9 (1), 0.8 (1), 0.7 (1), 0.6 (1), 0.5 (1), 0.4 (1), 0.3 (1), 0.2 (1), 0.1 (1), 0.0 (1).

The bioreduction of ketone 1i (0.369 g, 2 mmol) by *Geotrichum candidum* CCT 1205 furnished (S)-2i (0.370 g, 99.2% yield) as colorless oil; m/z 25: 3.7 (1), 3.6 (2), 3.5 (1), 3.4 (100), 3.3 (1), 3.2 (1), 3.1 (9), 3.0 (1), 2.9 (1), 2.8 (1), 2.7 (1), 2.6 (1), 2.5 (1), 2.4 (1), 2.3 (1), 2.2 (1), 2.1 (2), 2.0 (1), 1.9 (1), 1.8 (1), 1.7 (1), 1.6 (1), 1.5 (1), 1.4 (1), 1.3 (1), 1.2 (1), 1.1 (1), 1.0 (1), 0.9 (1), 0.8 (1), 0.7 (1), 0.6 (1), 0.5 (1), 0.4 (1), 0.3 (1), 0.2 (1), 0.1 (1), 0.0 (1).

The bioreduction of ketone 1j (0.369 g, 2 mmol) by *Rhodotorula glutinis* CCT 2182 furnished (R)-2j (0.366 g, 96.4% yield) as colorless oil; m/z 25: 3.7 (1), 3.6 (2), 3.5 (1), 3.4 (100), 3.3 (1), 3.2 (1), 3.1 (9), 3.0 (1), 2.9 (1), 2.8 (1), 2.7 (1), 2.6 (1), 2.5 (1), 2.4 (1), 2.3 (1), 2.2 (1), 2.1 (2), 2.0 (1), 1.9 (1), 1.8 (1), 1.7 (1), 1.6 (1), 1.5 (1), 1.4 (1), 1.3 (1), 1.2 (1), 1.1 (1), 1.0 (1), 0.9 (1), 0.8 (1), 0.7 (1), 0.6 (1), 0.5 (1), 0.4 (1), 0.3 (1), 0.2 (1), 0.1 (1), 0.0 (1).

The bioreduction of ketone 1k (0.369 g, 2 mmol) by *Rhodotorula glutinis* CCT 2182 furnished (R)-2k (0.366 g, 98.0% yield) as colorless oil; m/z 25: 3.7 (1), 3.6 (2), 3.5 (1), 3.4 (100), 3.3 (1), 3.2 (1), 3.1 (9), 3.0 (1), 2.9 (1), 2.8 (1), 2.7 (1), 2.6 (1), 2.5 (1), 2.4 (1), 2.3 (1), 2.2 (1), 2.1 (2), 2.0 (1), 1.9 (1), 1.8 (1), 1.7 (1), 1.6 (1), 1.5 (1), 1.4 (1), 1.3 (1), 1.2 (1), 1.1 (1), 1.0 (1), 0.9 (1), 0.8 (1), 0.7 (1), 0.6 (1), 0.5 (1), 0.4 (1), 0.3 (1), 0.2 (1), 0.1 (1), 0.0 (1).
or nutrient broth 2 (yeast extract, malt extract, peptone) for *Rhodotorula glutinis* CCT 2182 a.

2.21. (S)-(+)-2-Chloro-1-(4-nitrophenyl)ethanol (S)-2j. The bioreduction of ketone 1j (0.399 g, 2 mmol) by *Geotrichum candidum* CCT 1205 furnished (R)-2j (0.395 g, 98.0% yield) a white solid, mp 87°C (lit. p.f. 87°C) [36]; [α]_D^25 ~32.6° (c 1, CHCl_3) [lit. +37.2°, c 2.0, CHCl_3 for S isomer, 98.2% ee] [33], giving an optical purity of >99% determined by GC using a chiral column; 1H and 13C NMR and IR spectra and MS analysis were identical to those observed with its (S) enantiomer.

2.22. (R)-(−)-2-Chloro-1-(4-nitrophenyl)ethanol (R)-2j. The bioreduction of ketone 1j (0.399 g, 2 mmol) by *Rhodotorula glutinis* CCT 2182 furnished (R)-2j (0.395 g, 98.0% yield) a white solid, mp 87°C (lit. p.f. 87°C) [36]; [α]_D^25 ~32.6° (c 1, CHCl_3) [lit. +37.2°, c 2.0, CHCl_3 for S isomer, 98.2% ee] [33], giving an optical purity of >99% determined by GC using a chiral column; 1H and 13C NMR and IR spectra and MS analysis were identical to those observed with its (S) enantiomer.

### Table 1: Asymmetric reduction of 2-halo-1-(4-substituted phenyl)-ethanones 1a-j mediated by *Geotrichum candidum* CCT 1205 and *Rhodotorula glutinis* CCT 2182.

| Ketone | Microorganism | T (°C) | Alcohol | Yield (%) | [α]_D^25 |
|--------|---------------|--------|---------|-----------|----------|
| 1a     | *Geotrichum candidum* | 28     | (S)-2a  | 96.4      | +40.0    |
| 1b     | "             | 28     | (S)-2b  | 95.1      | +38.7    |
| 1c     | "             | 28     | (S)-2c  | 96.0      | +48.3    |
| 1d     | "             | 28     | (S)-2d  | 98.0      | +19.8    |
| 1e     | "             | 28     | (S)-2e  | 97.6      | +25.0    |
| 1f     | "             | 28     | (S)-2f  | 99.4      | +35.0    |
| 1g     | "             | 28     | (S)-2g  | 95.0      | +48.3    |
| 1h     | "             | 28     | (S)-2h  | 96.4      | +48.3    |
| 1i     | "             | 28     | (S)-2i  | 99.2      | +41.4    |
| 1j     | "             | 28     | (S)-2j  | 97.0      | +32.6    |
| 1a     | *Rhodotorula glutinis* | 30     | (R)-2a  | 99.0      | −40.4    |
| 1b     | "             | 30     | (R)-2b  | 97.0      | −38.7    |
| 1c     | "             | 30     | (S)-2c  | 95.3      | −48.3    |
| 1d     | "             | 30     | (R)-2d  | 97.8      | −19.7    |
| 1e     | "             | 30     | (R)-2e  | 98.0      | −25.0    |
| 1f     | "             | 30     | (R)-2f  | 97.7      | −34.9    |
| 1g     | "             | 30     | (R)-2g  | 94.2      | −48.3    |
| 1h     | "             | 30     | (R)-2h  | 95.7      | −48.3    |
| 1i     | "             | 30     | (R)-2i  | 98.0      | −41.5    |
| 1j     | "             | 30     | (R)-2j  | 98.0      | −32.6    |

*a* 18 h, 2 mmol of ketone/1.5 mL of EtOH was added to 15 g of yeast (wet weight)/400 mL of nutrient broth 1 (malt extract, peptone) for *Geotrichum candidum* or nutrient broth 2 (yeast extract, malt extract, peptone) for *Rhodotorula glutinis*. *b* ee > 99%. *c* See Materials and Methods for values and solvent.

Figure 1: Prelog rule for discrimination of the faces of carbonylic group by the enzymes.

3. Results and Discussion

The reduction of ethanones 1a-j was carried out in 5 mmol/L in a slurry of growing yeast of *Rhodotorula glutinis* CCT 2182 and *Geotrichum candidum* CCT 1205. These ethanones having substituted groups (electron withdrawing groups—EWG: −NO₂, −Br, −Cl; electron donating groups—EDG: −CH₃, −OCH₃) attached to position 4 of benzene ring were studied in order to investigate the influence of these groups in the bioreduction performed by these two microorganisms.
The reaction progress was monitored by GC analysis, and the yields and enantiomeric excesses are shown in Table 1. The reductions of 2-bromo-1-(4-substituted phenyl)ethanones 1a-e and 2-chloro-1-(4-substituted)-ethanones 1f-j mediated by \textit{Rhodotorula glutinis} CCT 2182 gave the corresponding halohydrins 2a-j with (R) configuration, while the halohydrins 2a-j with (S) configuration were obtained when \textit{Geotrichum candidum} CCT 1205 mediated the reduction of the ethanones 1a-j.

α-Haloacetophenones have been used as mechanistic probe in the reduction reactions of NADH-dependent horse liver alcohol dehydrogenase [37–40], for identification of reductants in sediments [41] and even in the whole cells [42]. This probe enables the differentiation between reduction processes which proceed through hydride transfer (H⁻) or by a multistep electron transfer (e⁻, H⁺, e⁻ as has been suggested). Acetophenone is the reduction product obtained by electron transfer, while optically active halohydrin is obtained when an enzyme mediates a hydride transfer process. In this work, the reductions of 1a-e proceed via hydride transfer mediated by an oxireductase, since halohydrins were obtained in high ee and no 4-substituted acetophenone was detected.

\textit{Rhodotorula glutinis} gives products following the Prelog rule [43], which predicts that, in general, hydrogen transfer from NAD(P)H to the prochiral ethanones 1a-j occurs to the face of carbonylic group shown in Figure 1, taking into account that the aryl group is larger than the –CH₂Br and –CH₂Cl groups. On the contrary, the \textit{Geotrichum candidum} gives anti-Prelog halohydrins.

The excellent results and complementary enantioselectivities of the produced halohydrins obtained by using \textit{Rhodotorula glutinis} CCT 2182 and \textit{Geotrichum candidum} CCT 1205 in reduction of ethanones 1a-j are remarkable and highlight the potential of such approach to obtain separately the two isomers of the 1,2-aminoalcohols, by reaction of the easily obtainable epoxy with the appropriated amine (Scheme 2), as an alternative to the approach using the...
reduction of $\alpha$-azido-para-substituted acetophenones mediated by those microorganisms [28]. The separate synthesis of two enantiomers is important since the FDA Guidance for Development of New Stereoisomeric Drugs [44] says that “to evaluate the pharmacokinetics of a single enantiomer or mixture of enantiomers, manufacturers should develop quantitative assays for individual enantiomers in in vivo samples early in drug development.” However, the products of biotransformation of 1b-e and 1g-j using *Rhodotorula glutinis* CCT 2182 may be used as important starting material for the preparation of the known pharmaceuticals products with (R) configuration: Eliprodil from halohydrins 2b and 2g; Tembamide from halohydrins 2c and 2h; Aegeline from halohydrins 2d and 2i; Nifenalol from halohydrins 2e and 2j (Figure 2).

4. Conclusions

The use of *Rhodotorula glutinis* CCT 2182 and *Geotrichum candidum* CCT 1205 in bioreduction reaction of 2-halo-1-(4-substituted phenyl)-ethanones results in an important chiral halohydrins in high ee, excellent yield, and complementary enantioselectivity. These halohydrins may be used as intermediates in the synthesis of optically active substituted styrene oxides and aminoalcohols which have numerous industrial applications.

Acknowledgments

The authors thank FAPESP and CNPq for financial support.

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