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Synthesis of optically active α-bromohydrins via reduction of α-bromoacetophenone analogues catalyzed by an isolated carbonyl reductase

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ABSTRACT

Enantiomerically pure (*S*)-α-bromohydrins were prepared by the reduction of α-bromoacetophenone analogues catalyzed by an isolated carbonyl reductase from *Candida magnolia* with high yield and excellent enantiomeric excess when methyl *tert*-butyl ether was employed as the co-solvent, while avoiding the formation of by-products. This provides a new approach to access these chiral α-bromohydrins which are of pharmaceutical importance.

1. Introduction

Enantiomerically pure halohydrins are widely employed as synthetic building blocks for optically active molecules in pharmaceutical industries,[1] such as adrenergic receptor agonists, bronchodilators, anti-depressants, and HIV-1 protease inhibitors.[2–8] Both chemical and biocatalytic methodologies have been developed in order to obtain enantiomerically pure halohydrins.[9–11] Among them, the asymmetric reduction of α-haloacetophenones provides a straightforward approach to access these compounds.[12,13] In the synthesis of most adrenergic receptor agonists and other structurally-related compounds, bromohydrins should be a better choice than chlorohydrins, because the bromo group can be more readily substituted by an amino group or other nucleophiles, and cyclized to a five or six membered ring or epoxide.[14–16] Although the asymmetric reduction of α-haloacetophenones by organocatalysis, transition metal-based catalysis and biocatalysis have been greatly explored, studies have been mainly focused on α-chloroacetophenones.[17–19] There have been a few reports on the asymmetric reduction of α-bromoacetophenone and its analogues with moderate enantiomeric excess and low yield via whole cell catalysis reduction.[20–27] It has been reported that the whole cell reduction of α-bromoacetophenones was usually contaminated by the formation of by-products such as an α-chlorohydrin, phenylethandiol, acetophenone, and phenylethanol (Scheme 1),[20,22] because the bromo group could be substituted by a hydroxyl or chloride ion in the culture medium, or lost via electron transfer to give an acetophenone, which in turn could be reduced.[20,22] In this context, an anionic surfactant was used in an argon atmosphere to improve the efficiency of the microbial reduction of some α-bromoacetophenones, and thus enhance the yield and enantiomeric purity of the products.[28] However, the enantiomeric excess of the product alcohol still needs to be improved and the reduction must be conducted under an inert atmosphere. As a result, an efficient asymmetric reduction of α-bromoacetophenones still presents a worthwhile challenge in organic synthesis.

Since the use of isolated enzymes can simplify the components of the reaction mixtures, we envisioned that it might be a promising way to prevent the formation of by-products. Therefore, we screened several carbonyl reductases available in our laboratory using α-bromoacetophenone **1** as the substrate and found that a carbonyl reductase from *Candida magnolia* (**CMCR**) catalyzed the reduction of α-bromoacetophenone to (*S*)-2-bromo-1-phenylethanol with high yield. We thus examined the capability of this enzyme toward the reduction of other α-bromoacetophenone analogues, and the results are presented herein.

2. Results and discussion

The reduction of α-bromoacetophenones by the carbonyl reductase **CMCR** was studied using a NADPH regeneration system consisting of D-glucose dehydrogenase (**GDH**) and D-glucose (Scheme 2). The conversion and enantioselectivity were determined by chiral HPLC analysis. Due to the poor solubility of α-bromoacetophenones in a potassium phosphate buffer, the reduction conditions were optimized by employing 2-bromo-1-(4-methylphenyl)ethanone **2** and 2-bromo-1-(4-fluorophenyl)ethanone **9** as substrates in the potassium phosphate buffer with both hydrophilic and hydrophobic organic solvents. The results are shown in Table 1. The enzyme could tolerate both hydrophilic and hydrophobic organic solvents to some extent. For 2-bromo-1-

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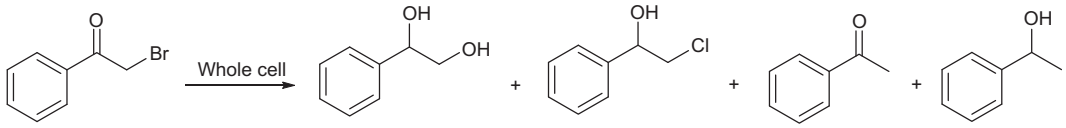
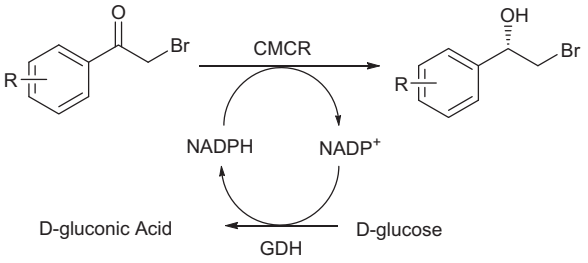


Scheme 1. Biotransformation of α-bromoacetophenone with whole cells of *Aspergillus. sydowii* Ce19.



Scheme 2. Reduction of α-bromoacetophenones catalyzed by **CMCR** with a cofactor recycle system of **GDH** and D-glucose.

Table 1
CMCR-catalyzed reduction of 2-bromo-1-(4-methylphenyl)ethanone **2** and 2-bromo-1-(4-fluorophenyl)-ethanone **9** in reaction media with different co-solvents

Solvent in buffer[a]	Conversion[b] (%)	
	Ketone **2**[c]	Ketone **9**[d]
No organic solvent	91	37
DMSO	95	61
MeOH	92	67
iso-PrOH	94	60
Methyl *tert*-butyl ether	70	72
iso-Propyl ether	—[e]	65
Ethyl acetate	46	15
Butyl acetate	44	17

[a] Potassium phosphate buffer (100 mM, pH 7.0) containing 10% (v/v) of organic solvent.
[b] Determined by HPLC analysis.
[c] Reaction time was 16 h.
[d] Reaction time was 3 h.
[e] Not determined.

(4-methylphenyl)ethanone, the addition of water-miscible solvents such as dimethylsulfoxide, methanol, or *iso*-propanol had a minimal effect on enzyme activity, while water-immiscible solvents decreased the conversion of 2-bromo-1-(4-methylphenyl)ethanone to (*S*)-2-bromo-1-(4-methylphenyl)ethanol. The conversion of 2-bromo-1-(4-fluorophenyl)ethanone in a potassium phosphate buffer without organic solvents was low, with only 50% conversion being observed after 16 h. This might be due to the poor solubility of 2-bromo-1-(4-fluorophenyl)ethanone in the buffer. In addition to water-miscible solvents, such as dimethylsulfoxide, methanol and *iso*-propanol, the water-immiscible solvents, such as methyl *tert*-butyl ether and *iso*-propyl ether, also benefited the reduction of 2-bromo-1-(4-fluorophenyl)ethanone to some extent.

The activity of the carbonyl reductase from *Candida magnoliae* toward the reduction of α-bromoacetophenone analogues was determined by spectrophotometrically measuring the rate for the oxidation of NADPH as described in the Experimental, and the results are shown in Table 2. From these results it can be seen that the substituents on the α-bromoacetophenone derivatives greatly affected the enzyme catalytic activity. Electron-withdrawing substituents enhanced the enzyme activity, while substrates with electron-donating substituents were less active. The same trend was also observed for the reduction of acetophenone analogues to the corresponding alcohols catalyzed by **CMCR**.[29]

Since the bioreduction of 2-bromo-1-(4-methylphenyl)ethanone catalyzed by **CMCR** proceeded cleanly with high conversion when methyl *tert*-butyl ether was used as a co-solvent in the reaction medium, the reductions of several α-bromoacetophenones were studied under the same reaction conditions, and the results are summarized in Table 2. The products were isolated by extraction with methyl *tert*-butyl ether in good to excellent yields. Chiral HPLC analysis indicated that the enantiomeric excesses of all the α-bromohydrins were greater than 99%. Itoh et al. have reported that a NADH-dependent phenylacetaldehyde reductase (**PAR**) from *Corynebacterium* strain ST-10 and a *Leifsonia* alcohol dehydrogenase (**LSADH**) catalyzed the reduction of 4-bromo-3-oxo-butanoate to give 4-bromo-3-hydroxybutanoate in the (*R*)- and (*S*)-form,[30,31] respectively. In the case of **PAR**, the reaction was carried out on a 1 mL scale without reporting a yield.[30] For **LSADH**, (*S*)-4-bromo-3-hydroxybutanoate was obtained in only 35% yield, although the conversion was 100%.[31] Herein, **CMCR** catalyzed a cleaner reduction of α-bromoacetophenones in the bi-phasic medium than the

Table 2
Bioreduction of various α-bromoacetophenone analogues catalyzed by **CMCR**

Ketone[a]	Specific activity[b]	Isolated yield (%)	Ee[c] (%)
2-Bromo-1-phenylethanone **1**	203	92	>99
2-Bromo-1-(4-methylphenyl)ethanone **2**	278	81	>99
2-Bromo-1-(3-methoxyphenyl)ethanone **3**	95	84	>99
2-Bromo-1-(4-methoxyphenyl)ethanone **4**	21	85	>99
2-Bromo-1-(3-nitrophenyl)ethanone **5**	847	91	>99
2-Bromo-1-(4-nitrophenyl)ethanone **6**	329	79	>99
2-Bromo-1-(4-chlorophenyl)ethanone **7**	1438	82	>99
2-Bromo-1-(3,4-dichlorophenyl)ethanone **8**	1279	84	>99
2-Bromo-1-(4-fluorophenyl)ethanone **9**	597	89	>99

[a] The reaction was carried out in a potassium phosphate buffer (100 mM, pH 7.0) containing 10% (v/v) of methyl *tert*-butyl ether.
[b] The unit of specific activity is nmol mg^{-1} min^{-1}.
[c] Determined by chiral HPLC analysis.

previously reported whole-cell reaction.[20] In spite of this improvement, it should also be noted that, from the point view of an industrially practical production, this method is not yet efficient enough in terms of substrate concentration, enzyme efficiency and so on.

3. Conclusion

The use of an isolated carbonyl reductase from *Candida magnolia* and a D-glucose dehydrogenase/D-glucose cofactor regeneration system in a bi-phasic reaction medium effectively prevents the side-reactions previously observed for the reduction of α-bromoacetophenones, leading to enantiomerically pure (*S*)-α-bromohydrins in high yields. This offers a new method to access this type of pharmaceutically interesting chiral alcohol, although the efficiency needs to be further improved upon.

4. Experimental

4.1. General

Carbonyl reductase from *Candida magnolia* and D-glucose dehydrogenase was prepared as described previously.[29,30,32] All the ketones were purchased from Sigma–Aldrich and the cofactors were obtained from Codexis. The racemic alcohol standards were prepared by reduction of the corresponding ketones with sodium borohydride. Chiral HPLC analysis was performed on an Agilent 1200 series high-performance liquid chromatography system with AD column (25 cm × 4.6 mm, Dacel Inc.). The enzyme activities toward the reduction of ketones were assayed using a SpectraMax M2 microplate reader (Molecular Devices). The ^{1}H NMR was measured by Brucker Avance 600 using $CDCl_3$ as the solvent. The optical rotation was recorded on an Anton paar MCP 200.

4.2. Activity assay for the reduction of α-bromoacetophenones catalyzed by CMCR

The activity of carbonyl reductase from *Candida magnoliae* toward the reduction of α-bromoacetophenones was determined by spectrophotometrically measuring the oxidation of NADPH at 340 nm (ϵ = 6.22 mM^{-1} cm^{-1}) in the presence of an excess amount of ketones. The activity was measured at room temperature in a 96-well plate, in which each well contained ketone (4.0 mM) and NADPH (0.6 mM) in potassium phosphate buffer (100 mM, pH 6.5, 180 μL). The reaction was initiated by the addition of the carbonyl reductase (20 μL solution containing 4–40 μg of enzyme). The specific activity was defined as the number of nanomoles of NADPH converted in 1 min by 1 mg of enzyme (nmol min^{-1} mg^{-1}).

4.3. CMCR-catalyzed reduction of 2-bromo-1-(4-methylphenyl) ethanone 2 and 2-bromo-1-(4-fluorophenyl)ethanone 9 in reaction media with different co-solvents

2-Bromo-1-(4-methylphenyl)ethanone **2** and 2-bromo-1-(4-fluorophenyl)-ethanone **9** were chosen as substrates for the reduction in reaction media with different co-solvents as listed in Table 1. The reaction procedure was as follows: D-glucose (36 mg), D-glucose dehydrogenase (4 mg), NADP (2 mg), ketoreductase (**CMCR**, 2 mg) and 2-bromo-1-(4-methylphenyl)ethanone (0.04 mmol, dissolved in 0.1 mL of organic solvent) were mixed with 0.9 mL of potassium phosphate buffer (100 mM, pH 6.5). The mixture was shaken for 16 h (or 3 h) at 30 °C for 2-bromo-1-(4-methylphenyl)ethanone (or 2-bromo-1-(4-fluorophenyl)ethanone), and then extracted with methyl *tert*-butyl ether (0.8 mL). The organic extract was dried over anhydrous sodium sulfate and subjected to HPLC analysis to measure the conversion and enantiomeric excess.

4.4. Synthesis of chiral -bromohydrins

The synthesis of various α-bromohydrins was carried out as follows: D-glucose (540 mg), D-glucose dehydrogenase (15 mg), NADPH (5 mg), and ketoreductase (CMCR, 60 mg) were mixed in a potassium phosphate buffer (27 mL, 100 mM, pH 6.5). The mixture was added to a ketone solution (100 mg in 3 mL of MTBE). The mixture was stirred at 30 °C for 12–16 h until the conversion was complete. The mixture was then extracted with methyl *tert*-butyl ether. The organic extract was dried over anhydrous sodium sulfate and removal of the solvent gave the product alcohol, which was identified by ^{1}H NMR and comparison of the retention time by chiral HPLC analysis with authentic samples. (*S*)-2-Bromo-1-phenylethanol **10.**[33] ^{1}H NMR ($CDCl_3$), δ: 2.58 (s, 1H), 3.58 (t, 1H, $^2J_{H-H}$ = 9 Hz), 3.68 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 3.0 Hz), 4.96 (dd, 1H, $^3J_{H-H}$ = 6.6 Hz, $^3J_{H-H}$ = 2.4 Hz), 7.39 (m, 5H). $[\alpha]_D^{20} = +13.1$ (*c* 0.62, methanol). (*S*)-2-Bromo-1-(4-methylphenyl)ethanol **11.**[34] ^{1}H NMR ($CDCl_3$), δ: 2.25 (s, 3H), 2.58 (br s, 1H), 3.54 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 9.0 Hz), 3.62 (dd, 1H, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 3.6 Hz), 4.89 (dd, 1H, $^3J_{H-H}$ = 9.0 Hz, $^3J_{H-H}$ = 3.0 Hz), 7.19 (d, 2H, $^3J_{H-H}$ = 7.8 Hz), 7.27 (d, 2H, $^3J_{H-H}$ = 7.8 Hz). $[\alpha]_D^{20} = +20.0$ (*c* 1.92, methanol). (*S*)-2-Bromo-1-(3-methoxyphenyl)ethanol **12.**[35] ^{1}H NMR ($CDCl_3$), δ: 2.60 (br s, 1H), 3.54 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 9.0 Hz), 3.63 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 3.6 Hz), 3.82 (s, 3H), 4.89 (d, 1H, $^3J_{H-H}$ = 9.0 Hz), 6.87 (t, 1H), 6.95 (d, 2H,) 7.28 (t, 1H, $^3J_{H-H}$ = 8.4 Hz). $[\alpha]_D^{20} = +19.7$ (*c* 2.0, methanol). (*S*)-2-Bromo-1-(4-methoxyphenyl)ethanol **13.**[34] ^{1}H NMR ($CDCl_3$), δ: 2.66 (s, 1H), 3.54 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 9.0 Hz), 3.63 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 3.6 Hz), 3.82 (s, 3H), 4.89 (d, 1H, $^3J_{H-H}$ = 9.0 Hz), 6.87 (t, 1H), 6.95 (d, 2H,) 7.28 (t, 1H, $^3J_{H-H}$ = 8.4 Hz). $[\alpha]_D^{20} = +29.0$ (*c* 1.88, methanol). (*S*)-2-Bromo-1-(3-nitrophenyl)ethanol **14.**[36] ^{1}H NMR ($CDCl_3$), δ: 2.81 (s, 1H), 3.56 (dd, 1H, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 8.4 Hz), 3.69 (dd, 1H, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 3.6 Hz),5.04 (d, 1H, $^3J_{H-H}$ = 8.4 Hz), 7.57 (t, 1H, $^3J_{H-H}$ = 8.4 Hz), 7.74 (d,1H, $^3J_{H-H}$ = 7.8 Hz), 8.18 (d, 1H, $^3J_{H-H}$ = 8.4 Hz). 8.29 (s, 1H). $[\alpha]_D^{20} = +18.5$ (*c* 1.36, methanol). (*S*)-2-Bromo-1-(4-nitrophenyl)ethanol **15.**[27,33,34] ^{1}H NMR ($CDCl_3$), δ: 2.76 (br s, 1H), 3.53 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 8.4 Hz), 3.67 (dd, 1H, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 3.6 Hz), 5.04 (d, 1H, $^3J_{H-H}$ = 5.4 Hz), 7.58 (d, 2H, $^3J_{H-H}$ = 8.4 Hz), 8.24 (d, 2H, $^3J_{H-H}$ = 8.4 Hz). $[\alpha]_D^{20} = +20.4$ (*c* 1.6, methanol). (*S*)-2-Bromo-1-(4-chlorophenyl)ethanol **16.**[33] ^{1}H NMR ($CDCl_3$), δ: 2.68 (br s, 1H), 3.51 (t 1H, $^2J_{H-H}$ = 10.2 Hz), 3.61 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 3.0 Hz), 4.91 (d, 1H, $^3J_{H-H}$ = 8.4 Hz), 7.34 (q, 4H, $^3J_{H-H}$ = 15.6 Hz, $^3J_{H-H}$ = 8.4 Hz). $[\alpha]_D^{20} = +21.9$ (*c* 1.28, methanol). (*S*)-2-Bromo-1-(3,4-dichloro-phenyl)ethanol **17.**[37] ^{1}H NMR ($CDCl_3$), δ: 2.70 (br s, 1H), 3.51 (t 1H, $^2J_{H-H}$ = 9.0 Hz), 3.61 (dd, 1H, $^2J_{H-H}$ = 9.6 Hz, $^3J_{H-H}$ = 2.4 Hz), 4.89 (dd, 1H, $^3J_{H-H}$ = 8.4 Hz, $^3J_{H-H}$ = 3.0 Hz), 7.21 (d, 1H, $^3J_{H-H}$ = 8.4 Hz), 7.44 (d,1H, $^3J_{H-H}$ = 8.4 Hz), 7.51 (s, 1H). $[\alpha]_D^{20} = +16.1$ (*c* 0.82, methanol). (*S*)-2-Bromo-1-(4-fluorophenyl)ethanol **18.**[38] ^{1}H NMR ($CDCl_3$), δ: 2.65 (s, 1H), 3.51 (dd, 1H, $^2J_{H-H}$ = 10.2 Hz, $^3J_{H-H}$ = 9 Hz), 3.61 (dd, 1H, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 3.6 Hz), 4.91 (d, 1H, $^3J_{H-H}$ = 8.4 Hz), 7.06 (t, 2H, $^3J_{H-H}$ = 9 Hz), 7.58 (q, 2H, $^3J_{H-H}$ = 8.4 Hz, $^3J_{H-H}$ = 5.4 Hz). $[\alpha]_D^{20} = +16.1$ (*c* 1.4, methanol). The absolute configurations of the product alcohols **10**,[33] **11**,[34] **12**,[34] **15**,[27,33,34] and **16**[33] were determined by comparison of the sign of the specific rotation with those in the literature. For **13**,[35] **14**,[36] **17**[37] and **18**,[38] they were considered to have the same absolute configuration as those listed before because they exhibited the same sign of specific rotation. The enantiomeric excess was determined by chiral HPLC analysis.

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