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REGULAR ARTICLE

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Green synthesis of enantiopure (*S*)-1-(benzofuran-2-yl) ethanol by whole-cell biocatalyst

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Abstract

Optically active aromatic alcohols are valuable chiral building blocks of many natural products and chiral drugs. *Lactobacillus paracasei* BD87E6, which was isolated from a cereal-based fermented beverage, was shown as a biocatalyst for the bioreduction of 1-(benzofuran-2-yl) ethanone to (*S*)-1-(benzofuran-2-yl) ethanol with highly stereoselectivity. The bioreduction conditions were optimized using *L. paracase*i BD87E6 to obtain high enantiomeric excess (ee) and conversion. After optimization of the bioreduction conditions, it was shown that the bioreduction of 1-(benzofuran-2-yl)ethanone was performed in mild reaction conditions. The asymmetric bioreduction of the 1-(benzofuran-2-yl)ethanone had reached 92% yield with ee of higher than 99.9% at 6.73 g of substrate. Our study gave the first example for enantiopure production of (*S*)-1-(benzofuran-2-yl)ethanol by a biological green method. This process is also scalable and has potential in application. In this study, a basic and novel whole-cell mediated biocatalytic method was performed for the enantiopure production of (*S*)-1-(benzofuran-2-yl)ethanol in the aqueous medium, which empowered the synthesis of a precious chiral intermediary process to be converted into a sophisticated molecule for drug production.

KEYWORDS

(*S*)-1-(benzofuran-2-yl)ethanol, asymmetric bioreduction, chirality, *Lactobacillus paracasei* BD87E6, whole-cell biocatalysts

1 | INTRODUCTION

Enantiopure secondary alcohols are valuable and versatile precursors for the production of chiral drugs.[1] Benzofurans with numerous application areas are bicyclic ring structures.[2] Benzofuran derivatives are found in the chemical structure of many drugs, such as bufuralols potent nonselective β-blockers antagonists, and 2-substituted benzofuranes can also obstruct the HIV-1 opposite transcriptase or can be used as antiaging compounds.[3] Benzofuran carbinols show different biological activities, and its derivatives were investigated as antifungal or antibacterial agents; at the same time, these derivatives have found application area in chemical pesticides and cosmetic industries.[4] Because of these properties, it has attracted much attention in the last few years in pharmaceutical chemistry and organic synthesis. Limited studies related the asymmetric bioreduction of 1-(benzofuran-2-yl)ethanone have been reported. Thus, it is important to develop enantioselective green methods for the reduction of 1-(benzofuran-2-yl)ethanone to the corresponding chiral alcohols. For instance, Zhong and coworkers have improved a series of tridentate ferrocene-based diamine-phosphine sulfonamide ligands and applied them in the asymmetric reduction of ketones, affording (*R*)-benzofuran alcohol with a 98%

enantiomeric excess (ee) and a 99% yield.[5] Lu and coworkers demonstrated cobalt-catalyzed asymmetric hydrogenation of 1-(benzofuran-2-yl)ethanone with 93% ee using the chiral iminophenyl oxazolinylphenyl amines ligands.[6] The drawbacks of this method are the expensive chiral reagent and environmental pollution. The enantioselectivity of the product is related to the complexity of the ligands. Some transition metals need additional enantiomeric ligands to achieve high enantioselectivity, and the cost of transition metals limits the use of industrialization processes.[7] Therefore, the search for alternative biocatalytic processes for preparation of enantiomerically pure (*S*)-1-(benzofuran-2-yl) ethanol attracts more attention. An alternative way is the enantioselective reduction of prochiral compounds using enzymes or enzyme-containing cells.[8] In comparison with the general chemical approach for chiral secondary alcohols synthesis, the biocatalytic method is more preferable because of its high-substrate specificity, mild reaction conditions, and environmental sustainability. Biocatalysts took advantage of high chemo-, regio-, unsurpassed selectivity and observed the green principles.[9] Furthermore, the use of microbial whole cells with metabolic activity as catalysts provides several merits over isolated enzymes, including the cofactor recycling in situ and better protecting target enzymes against inactivation, thereby significantly cutting down the process cost.[10] Whole-cell biocatalysts, rather than purified enzymes, may be more suitable for the large-scale production, because microbial whole cells used in production as catalysts contain multiple active enzymes and better protects desired enzymes against inactivation. Therefore, whole-cell biocatalysts provide an attractive alternative to selectively producing corresponding single enantiomers. In addition, the advantage of the in situ recycle of cofactors reduces the process cost, making it an increasingly attractive method for biocatalysts.[10-12] Asymmetric bioreduction of 2-acetylbenzo[b]furan with yeast biocatalyst gave (*S*)-corresponding alcohol with a moderate ee (55%) and in a moderate yield (60%).[13] Paizs and coworkers obtained (*S*)-1-(benzofuran-2-yl)ethanol by 98.6% ee and 49% yield with kinetic resolution of racemic benzofuran alcohol using lipase biocatalysts.[14] Although this yield is good for kinetic resolution, it is low for asymmetric reduction. The *Rhizopus arrhizus* mediated bioreduction of 1-(benzofuran-2-yl)ethanone furnished 99.3% (*S*)-1-(benzofuran-2-yl)ethanol, with 91.7% ee.[15] In the literature, it has been reported that 1-(benzofuran-2-yl) ethanone is reduced to (*R*)-benzofuran alcohol by 95% ee and 47% yield with *Daucus carota* as biocatalyst.[16] In the present study, isolated *Lactobacillus paracasei* BD87E6[17] was employed as a whole-cell biocatalyst in the asymmetric bioreduction of 1-(benzofuran-2-yl) ethanone to (*S*)-1-(benzofuran-2-yl)ethanol in an aqueous medium (Figure 1).

Herein, we report the asymmetric bioreduction of 1-(benzofuran-2-yl)ethanone **1** to the (S)-1-(benzofuran-2-yl)ethanol **2** by *L paracasei* BD87E6 with 99.9% ee and 92% yields. Also, this is the first report on asymmetric bioreduction of 1-(benzofuran-2-yl)ethanone **1** using biocatalyst in the enantiopure form, excellent yield. Gram scale bioreduction of 1-(benzofuran-2-yl)ethanone **1** was performed to the (*S*)-1-(benzofuran-2-yl) ethanol **2** in enantiomerically pure form and excellent yield using *L. paracasei* BD87E6 as a biocatalyst. The effects of some key reaction parameters in terms of temperature, pH, incubation period and agitation speed on the ee, conversion, and yield were also optimized individually for the reduction reaction.

2 | MATERIALS AND METHODS

2.1 | General

The substrate, bacterial growth medium (MRS), and solvents were received from Fluka and Aldrich (purity of >99%). The progress of reaction was checked by TLC, using ethyl acetate: hexane (10:90, v/v) as the mobile phase. Purification of (S)-1-(benzofuran-2-yl)ethanol was performed by column chromatography filled with silica gel (0.063-0.2 mm), and the product was eluted with a mixture of hexane: ethyl acetate (85:15, v/v). HPLC analyses for substrate and product were performed on an Agilent 1260 system combined with UV and chiral detector. Reference sample of racemic alcohol **2** was prepared by reducing the ketone **1** with $NaBH_4$ in methanol at room temperature (RT). Optical rotation was determined with a Bellingham + Stanley, ADP220, 589-nm spectropolarimeter. The NMR spectra of the product were detected by a Bruker spectrometer (Ascend TM; Bruker Ltd., Germany). **(*S*)-1-(benzofuran-2-yl)ethanol**[18]: light yellow liquid, isolated yield 92%, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55-7.52 (m, 1H), 7.48-7.44 (m, 1H), 7.29-7.19 (m, 1H), 7.24-7.20 (m, 1H), 6.61 (s, 1H), 5.02 (q, J = 6.5, Hz, 1H), 2.19 (bs, 1H (OH)), 1.64 (d, J = 6.5, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.2, 154.7, 128.1, 124.2, 122.8, 121.1, 111.2, 101.8, 64.2, 21.4; $[\alpha]_D^{25}$

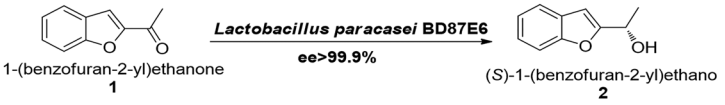

FIGURE 1 Asymmetric production of (*S*)-1-(benzofuran-2-yl)ethanol

= −19.8 (c = 0.5, $CHCl_3$) >99% ee, Lit. (*R*)-1-(benzofuran-2-yl) ethanol, $[\alpha]_D^{25}$ = 16.8 (c = 0.5, $CHCl_3$, for 84% ee)[18]; HPLC conditions: column of Chiralcel OD-H, mobile phase of *n*-hexane: isopropanol, 99:1 (v:v), flow rate of 0.5 mL min^{-1}, wavelength of 254 nm, t_R (*S*) 68.7 min. HPLC condition of substrate is the same as alcohol HPLC analysis condition and retention time: 19.4 minutes (Supporting Information).

2.2 | Bacterial strains and culture conditions

L. paracasei BD87E6 was formerly obtained from boza, a cereal-based fermented beverage, and preserved in our laboratory.[19] *L. paracasei* BD87E6 was propagated from their glycerol stocks by inoculation to 10-mL MRS broth medium (salt solution [$MgSO_4.7H_2O$ 11.5 % (w/v), pepton [Oxoid] 10 g L^{-1}, K_2HPO_4 2 g L^{-1}, yeast extract [Difco] 5 g L^{-1}, 2% glucose, $C_2H_3NaO_2.3H_2O$ 5 g L^{-1}, triamonium citrate 2 g l^{-1}], lab lemco [Oxoid] 8 g l^{-1}, $MnSO_4.4H_2O$ 2.8 % (w/v), Tween 80 1 ml l^{-1}, salt solution [$MgSO_4.7H_2O$ 11.5 % (w/v)) followed by 1 d growth at 30°C. From these samples, exponentially grown bacterial cells were inoculated to 1000-mL MRS medium at 10% concentration and incubated 2 days at 30°C under aerobic conditions, and following the successful growth, whole cell was dried by freeze-drying (Labconco, TR) and stored at RT without losing activity for three months.

2.3 | Asymmetric bioreduction process

A 50 mg of lyophilized *L. paracasei* BD87E6 was added in a 250-mL Erlenmeyer flask containing 100-mL MRS broth. The mixture was incubated at 150 rpm and 30°C for 2 hours. Subsequently, pH was adjusted to 6.0 with 1 N HCl. After 2 hours, 1 mmol of **1** was added to this mixture. The sample at conditions of asymmetric reduction was vibrated at 150 rpm and 30°C for 48 hours. After 48 hours, the bacteria cells were removed by centrifugation at 6000 × g for 5 minutes at 4°C. The liquid phase was saturated with NaCl, then extracted with dichloromethane. Organic phases were collected and washed with saturated sodium chloride salt solution and dried over anhydrous Na_2SO_4. The organic solvent was removed, and product was characterized using NMR analysis after purified by column chromatography on silica gel. The configuration was detected by the sign of specific rotation. The crude product was filtered with a small column containing silica gel, and the bioconversion was detected by chiral HPLC comparing the alcohol peaks with the ketone peak. After the product was purified, ee of the product was determined by chiral HPLC, and the yield was determined with pure product.

2.4 | Gram scale production of (*S*)-1-(benzofuran-2-yl)ethanol

After culture fermentation, the bioreduction was performed in 5-L Erlenmeyer flask using 1500 mL of MRS broth, 500-mg dry biocatalyst cells, and 6.73-g 1-(benzofuran-2-yl)ethanone under the optimized conditions, as mentioned above asymmetric bioreduction process.

3 | RESULTS AND DISCUSSION

Enantiopure alcohols are precursors for synthesis of many molecules, and the synthesis of these alcohols with biocatalytic method is very important. Functional group of chiral secondary alcohols could be converted into beneficial groups, which can be used as other pharmaceutical precursors, without racemization.[20] The study on optimization condition for biocatalysts is an important topic for improving the bioprocess efficacy.[21] The green production of (*S*)-1-(benzofuran-2-yl) ethanol catalyzed by *L. paracasei* BD87E6 was optimized in terms of several key optimization conditions, agitation speed, incubation period, temperature, and pH (Table 1). It is well-known that pH has an important role in the process of biocatalytic reduction using whole-cells biocatalyst. The optimization of pH for the bioreduction of keto compound **1** to **2** was investigated at pH range from 4.5 to 7.5. The bioreduction reactions were conducted using 1 mmol of **1** and 50-mg dry *L. paracasei* BD87E6 in RT, 24 hours and 100 rpm (Table 1). Varying the pH of the reaction system affects the permeability of the cell membrane, and the dissociation state of the groups necessary for the enzyme activity center and substrate, thus affecting the catalytic activity and enantioselectivity of the enzyme.[22] Enantioselectivity of the biocatalyst was markedly influenced by pH changes. The results indicate that pH of 6.0, maximum ee, and conversion were obtained (Table 1). Therefore, pH 6.0 was used for all further reactions as an optimal pH. Presumably, as the pH changes, the structure of the enzyme and, accordingly, the structure of the active site of the enzyme change. The interaction of the substrate with the active side of the enzyme is varied, and ee and conversion are different, and also, the solubility of the ketone can have influenced the enantioselectivity of the *L. paracasei* BD87E6.[23] Temperature, likewise, plays an important role in catalytic reduction mediated by microbial cells, including by affecting the activity of catalysts, the stability of enzyme

TABLE 1 Effect of pH, temperature, incubation period, and agitation speed on asymmetric reduction

pH			Temperature			Incubation Period			Agitation Speed		
pH	Conv. %[a]	ee %[b,c]	°C	Conv. %[a]	ee %[b,c]	h	Conv. %[a]	ee %[b,c]	rpm	Conv. %[a]	ee %[b,c]
4.5	66	56 (*S*)	25	87	87 (*S*)	24	94	99 (*S*)	100	96	99 (*S*)
5	72	63 (*S*)	28	82	84 (*S*)	48	96	99 (*S*)	150	97	>99 (*S*)
5.5	70	55 (*S*)	30	94	99 (*S*)	72	99	81 (*S*)	200	99	95 (*S*)
6	87	89 (*S*)	32	72	75 (*S*)	96	99	65 (*S*)	250	99	58 (*S*)
6.5	77	80 (*S*)									
7	64	19 (*S*)									
7.5	27	15 (*S*)									

Note. Substrate 1 mmol.

[a]The bioconversion was determined by chiral HPLC.

[b]Determined by HPLC using Chiralcel OD-H column.

[c]Absolute configurations were determined by comparison of the sign of optical rotations relative to the values in the literature.

production, and reaction stereoselectivity.[24] The effects of the reaction temperature on the bioreduction was also examined. Therefore, the effect of different reaction temperatures ranging from 25°C to 32°C on conversion, and ee was investigated using pH 6.0, 100 rpm, 24 hours as reaction conditions and the results displayed in Table 1. As can be seen in Table 1, the conversion increased with the increment in the reaction temperature from 25°C to 32°C. However, the ee decreased slightly when the temperature was above 30°C. This decrease may be resulted from the local inactivation of enzyme in the cells at high temperature.

The best reaction temperature was determined 30°C. Therefore, 30°C temperature was used for all further reactions as an optimized temperature. In biocatalytic reductions, incubation period can make a great difference on the conversion and ee.[25] The catalytic activity of *L. paracasei* BD87E6 for bioreduction of substrate **1** was studied in the pH 6.0, 30°C, 100 rpm and using different incubation period ranging from 24 to 96 hours (Table 1). As shown in Table 1, it was observed that as the incubation period increased, conversion rate of reaction increased; however, the ee was notably decreased. This reduction may be due to the decrease in the enzyme activity, suggesting reduce the selectivity of the enzyme. When incubation period of bioreduction in the 48 hours, maximum conversion and ee were obtained. Hence, incubation period of 48 hours was applied for next optimization reactions. The effects of the agitation speed on the bioreduction was also examined. The agitation speed can impact generally the particle transfer rate of substrates in the biocatalytic process.[23] Thus, it is important to investigate the effects of agitation speed on the bioreduction reaction. The catalytic activity of *L. paracasei* BD87E6 for bioreduction of substrate **1** was studied in the pH 6.0, 30°C, 48 hours and using different agitation speeds (from 100 to 250 rpm) as the reaction conditions (Table 1). Increasing agitation speed caused a rise in conversion and ee, but a sharp decrease is observed in ee after 150 rpm. The maximum bioconversion (>99%) and ee (>99%) was observed at 150 rpm, and therefore, 150 rpm was defined as the best agitation speed. When the concentration of catalyst increase, the amount of enzyme provided also increases, which can be conducive for the progress of the reaction and the improvement of the yield.[22] However, cell oxygen consumption also increases simultaneously, with the metabolites produced by cell metabolism likewise increasing within a short period, leading conversely to a decrease in the yield. Therefore, addition of the appropriate cell concentration has a significant effect in improving the yield of the bioreduction. Thus, cell concentrations varying from 30 to 70-mg/100-mL dry cell weight were designed in order to ascertain the optimum concentration for the bioreduction of 1-(benzofuran-2-yl)ethanone to (*S*)-1-(benzofuran-2-yl)ethanol. The results revealed that the maximal yield for (*S*)-1-(benzofuran-2-yl)ethanol reached 92% at 50-mg dry cell weight with a greater than 99.9% ee of product.

3.1 | Gram-scale synthesis of (*S*)-1-(benzofuran-2-yl)ethanol (*S*)-2

To further increase the scope of the study, with the optimal conditions in hand (pH 6.0, 30°C, 48 h, and 150 rpm), we carried out the gram scale reduction of 1-(benzofuran-2-yl)ethanone (**1**) (Figure 2). High gram-scale synthesis of (*S*)-1-(benzofuran-2-yl)ethanol (**2**) was carried out in a 1.5-L scale in the 5-L Erlenmeyer flask.

Asymmetric reduction in the gram scale using biocatalysts, the substrate concentration is very important.

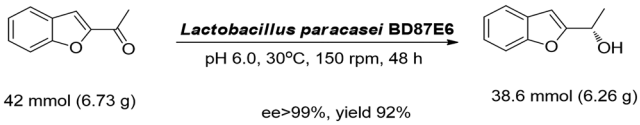

FIGURE 2 Gram-scale synthesis of (*R*)-2-methyl-1-phenylpropan-1-ol

In accordance with this information, various reduction reactions have been made using different substrate concentrations in the gram scale under optimized reduction conditions. For instance, asymmetric reduction of **1** (50 mmol) after 56 hours resulted in full conversion; however, the ee of the product was markedly decreased (77%). This means that higher concentration of substrate likely causes the loss of enzyme activity, owing to substrate toxicity and inhibition as reported previously.[26] The best result was obtained when 42 mmol (6.73 g) substrate was used. The asymmetric reduction of the substrate had reached 92% yield with an ee of greater than 99.9% at 6.73 g of 1-(benzofuran-2-yl)ethanone; the reaction was carried out at pH 6.5, 30oC, 150 rpm, and 48 hours using *L. paracasei* BD87E6 as a whole-cell biocatalyst. The configuration of the obtained product has occurred with respect to the Prelog rule, the pro-*R* hydride of NADPH is given to the *Re* face of the substrate to produce on *S* alcohol.[27] Aqueous solutions are considered as a classic reaction solution for biocatalytic reaction. Unfortunately, industrial attractive substrates usually are organic compounds. Water sometimes is a not a convenient solvent for most organic reactions even though it is considered as a solvent for life. Organic solvents are often required to increase the solubility of the hydrophobic substrate. But rapid denaturation of enzymes occurs when the volume fraction of most water-miscible solvents exceeds 20% to 50% (v/v). In our study, we did not use organic solvent, and on the basis of the results from key parameters optimized in a green synthesis method, we got a 92% yield of product at 42-mmol substrate concentration with enantiopure form of (*S*)-1-(benzofuran-2-yl)ethanol. The yield of benzofuran alcohol obtained with kinetic resolution in the literature is good, but this yield is low compared with asymmetric reduction.[14] Moreover, 50% of the unwanted enantiomer always occurs at kinetic resolution. Aldabalde et al performed the asymmetric reduction of substrate **1** using the *D. carota* biocatalyst in a shorter reaction time than our study, but their ee and yield were lower than our yield and ee.[16] Salvi et al carried out the asymmetric reduction of substrate **1** using *R. arrhizus* biocatalyst in a longer reaction time, lower ee and yield than our study.[15] From an industrial point of view, it is very important to work on a large scale; the scale of these two studies in the literature is quite low compared with our study. This study is superior with regard to enantiomeric excess, reaction scale, conversion, and yield compared with the previous studies, which are using biocatalysts.[15,16]

4 | CONCLUSION

In the present study, a green biological method used to produce (*S*)-1-(benzofuran-2-yl)ethanol with *L. paracasei* BD87E6 was successfully developed. The findings were that of achieving the desired product in a single step by the whole-cell method. This study provides a useful strategy to efficient and economical approach in the synthesis of chiral carbinols. Meanwhile, the bioreduction was in an aqueous medium at mild conditions, and the ensuing processing was very simple. The results showed that *L. paracasei* BD87E6 containing a carbonyl reductase is a hopeful biocatalyst for the production of the chiral drug precursors. In the present study, we successfully developed a green process for the efficient asymmetric bioreduction of 1-(benzofuran-2-yl)ethanone to its (*S*)-form benzofuran alcohol by *L. paracasei* BD87E6 whole-cells biocatalyst. Compared with the past reports, 1-(benzofuran-2-yl) ethanone **1** was reduced to (*S*)-1-(benzofuran-2-yl)ethanol **2** by biocatalyst in an excellent yield, ee, and conversion. Our study gave the first example for an enantiopure production of (*S*)-1-(benzofuran-2-yl)ethanol by a green biological method. *L. paracasei* BD87E6 biocatalyst is a promising for single-enantiomer production and can be used for industrial scale production.

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Supplementary Materials

Chiral and racemic HPLC spectrums, ^{1}H-NMR and ^{13}C-NMR spectra of product **2** could be found at supplementary data.

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SUPPORTING INFORMATION

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