Tetrahedron xxx (2017) 1–7

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chemoenzymatic synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* species and sulfoxidation with chiral titanium complexe

Baodong Cui, Min Yang, Jing Shan, Lei Qin, Ziyan Liu, Nanwei Wan, Wenyong Han, Yongzheng Chen*

Generic Drug Research Center of Guizhou Province, School of Pharmacy, Zunyi Medical University, Zunyi, 563000, PR China

ARTICLE INFO

Article history:
Received 31 May 2017
Received in revised form
6 July 2017
Accepted 8 July 2017
Available online xxx

Keywords:
Biocatalysis
Titanium complexe
Two-step reaction
Sulfoxidation
β-Hydroxyl-sulfoxides

ABSTRACT

A two-step enantioselective synthetic strategy for the preparation of β-hydroxyl-sulfoxides has been described. With the enzymatic reduction of β-ketosulfides using *Pseudomonas monteilii* ZMU-T04 followed by the asymmetric sulfoxidation with Ti(O^iPr)$_4$/(*S*)-BINOL complexe, a wide range of corresponding β-hydroxyl-sulfoxide derivatives were smoothly obtained with excellent stereoselectivities (up to 99:1 dr and >99% ee). A plausible chelate structure of titanium complexe in the asymmetric sulfoxidation of β-hydroxyl-sulfides was also proposed on the basis of control experiments.

1. Introduction

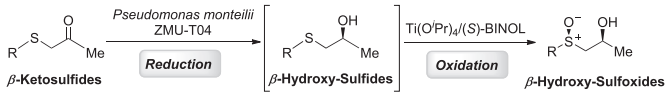
Endeavors toward the creation of chiral functional molecules from readily available materials are of continuing interest in organic chemistry. Particularly, asymmetric synthesis achieved by either chemocatalysis or biocatalysis is a highly active research field and has presented great success.[1] However sometimes either of these synthetic strategies might be hindered by the need for specially designed starting materials or by the intrinsic limiting reactivity of the single catalyst applied. This problem associated with the low efficiency of the single catalytic system can be compensated by the application of two-step reaction with two different catalysts. In this context, the two-step reaction with chemo-enzymatic catalysis have gained increasing attention due to its unprecedented level of efficiency in the asymmetric synthesis.[2,3]

Literature survey reveals that sulfur-containing chiral alcohols can serve as intermediates in the synthesis of biologically active compounds and naturally occurring products,[4] and this unique synthetic versatility is usually determined by the presence of a sulfur atom placed at an appropriate position from the hydroxyl group.[5] β-Hydroxyl-sulfoxides with the sulfoxide and hydroxyl groups at 1,3-positions well represent the privileged sulfur-containing chiral alcohols that have been widely used as key synthons in the asymmetric synthesis. Therefore, considerable efforts have focused on the development of creative strategies to access β-hydroxyl-sulfoxide derivatives. These strategies mainly include the biotransformation of β-ketosulfides,[6] chemical sulfoxidation followed by reduction of β-ketosulfides,[7] and the stereoselective reduction of chiral β-ketosulfoxides promoted by samarium diiodide.[4e,8] However, the two-step reaction involving enzymatic reduction followed by organometal promoted asymmetric sulfoxidation of β-ketosulfides for the synthesis of chiral β-hydroxyl-sulfoxides has not been exploited although a few chemo-enzymatic protocols have been reported.[5b,9]

Inspired by these achievements and the sulfoxidation promoted by titanium complexe,[7,10] as well as our successful exploration of oxidation and reduction reactions mediated by *Pseudomonas monteilii* species,[11] we envisioned an alternative chemo-enzymatic strategy for preparation of the chiral β-hydroxyl-sulfoxide derivatives. Firstly, the *Pseudomonas monteilii* ZMU-T04 mediated asymmetric reduction of β-ketosulfides produced the chiral β-hydroxyl-sulfide intermediates.

* Corresponding author. Tel.: +86 851 28642336; fax: +86 851 28609726.
E-mail address: yzchen@zmc.edu.cn (Y. Chen).

http://dx.doi.org/10.1016/j.tet.2017.07.014
0040-4020/



Scheme 1. Design for the synthesis of chiral β-hydroxyl-sulfoxides.

Subsequently, the chiral β-hydroxyl-sulfides were oxidized to the final enantiomerically pure β-hydroxyl-sulfoxides with $Ti(O^iPr)_4$/(*S*)-BINOL complexe (Scheme 1). Herein, we will disclose our research results on this subject.

2. Results and discussion

Initial experiments were performed with 1-((4-chlorophenyl) thio)propan-2-one **1a**, cell suspension of *Pseudomonas monteilii* species and Na_2HPO_4-KH_2PO_4 buffer for 24 h, and selected reaction results for the asymmetric reduction of β-ketosulfides **1** are shown in Table 1. The screening of our laboratory's different strains from *Pseudomonas monteilii* ZMU-T01 to ZMU-T17 revealed that ZMU-T04 strain gave the best results, providing (*S*)-β-hydroxyl-sulfide **2a** with 97% ee and 96% conversion of model substrate **1a** (entry 2). Other strains, including ZMU-T05, ZMU-T06 and ZMU-T17, showed lower activity for the asymmetric reduction of **1a** despite showing satisfactory enantioselectivities (entries 3, 4 and 7). A boost in enantioselectivity was not achieved by replacing the medium from M9 to LB (entry 8). Then the effect of substrate concentration of **1a** was explored. The reaction results revealed that increasing of the substrate concentration of **1a** had slight positive effect on the enantioselectivity but was not beneficial for the conversion of substrate **1a** to **2a** (entries 9–11). The following investigation of cell concentration of *Pseudomonas monteilii* ZMU-T04 identified 50 cdw g/L as the optimal catalyst loading, and the desired product **2a** was obtained in >99% ee with >99% conversion of substrate **1a** (entry 12).

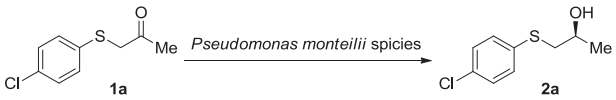
After establishment of the optimal reaction conditions (Table 1, entry 12), we moved on to explore the scope of the asymmetric bio-reduction of β-ketosulfides **1** (Table 2). We were pleased to find that the high efficiency demonstrated by *Pseudomonas monteilii* ZMU-T04 in the model reaction could be sustainable for the asymmetric reduction of a broad range of β-ketosulfides. Generally, aromatic β-ketosulfides bearing substituents at the *ortho*-, *meta*-, and *para*-positions gave the desired β-hydroxyl-sulfides with excellent enantioselectivities (products **2a**, **c-q**). The electronic nature of the aromatic substituents had no obvious impact on efficiencies and enantioselectivities. Products were generated with similar results when β-ketosulfides with electron-donating (**1c-f** and **1k-m**) and electron-withdrawing substituents (**1a, 1g-j** and **1n-q**) on the phenyl moiety were applied. Notably, the bulky 2-naphthyl substituted β-ketosulfide **1r** also participated successfully in the reaction and gave rise to the corresponding β-hydroxyl-sulfide **2r** with 92% ee and >99% conversion of **1r** (entry 18).

Having ascertained the scope of the asymmetric bio-reduction of a variety of β-ketosulfides **1**, we turned our attention to investigate the generality of the asymmetric sulfoxidation of β-hydroxyl-sulfides **2** promoted by $Ti(O^iPr)_4$/(*S*)-BINOL complexe with ^{t}BuOOH as the oxidant. As shown in Table 3, all the chiral β-hydroxyl-sulfides **2** could be employed successfully into the following asymmetric sulfoxidation reaction and furnished the optically active β-hydroxyl-sulfoxides **3** with moderate to excellent diastereoselectivities and overall excellent enantioselectivities. However, lower yields for products **3e** and **3k-o** were provided due to the excessive sulfoxidation to sulfones (entries 5 and 11–15). In addition, the sterically demanding β-hydroxyl-sulfides **2c**, **2d** and **2f-j** gave the inferior diastereoselectivities (entries 3, 4 and 6–10). Similarly, the bulky 2-naphthyl substituted β-hydroxyl-sulfide **2r** also participated well in the reaction and offered the corresponding β-hydroxyl-sulfoxide **3r** in 91% yield with >99% ee but only 84:16 dr (entry 18).

The absolute configuration of the major stereoisomer **3b** could be assigned as (*CS*, *SS*) by HPLC comparison with the previous literature report.[9] Interesting, another diastereomer **3a'** also could be obtained in 71% yield with 99:1 dr and 99% ee by changing the absolute configuration of BINOL (Scheme 2).

To explain the transition state of titanium complexe in the asymmetric sulfoxidation of β-hydroxyl-sulfides **2**, three control experiments were performed. Firstly, the asymmetric sulfoxidation of **2a** (99% ee) provided the β-hydroxyl-sulfoxide **3a** in 61% yield

Table 1
Optimization of Reaction Conditions for Asymmetric Reduction of β-ketosulfides **1**.[a]

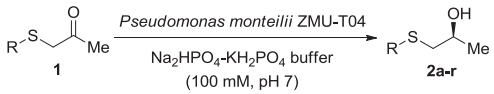


Entry	Strain species	Cell concentration (cdw g/L)	Concentration of **1a** (mM)	Conversion of **1a**[b] (%)	**2a**/ee[c] (%)
1	ZMU-T01	30	5	67	94
2	ZMU-T04	30	5	96	97
3	ZMU-T05	30	5	5	90
4	ZMU-T06	30	5	48	85
5	ZMU-T07	30	5	99	94
6	ZMU-T14	30	5	89	99
7	ZMU-T17	30	5	7	73
8[d]	ZMU-T04	30	5	97	87
9	ZMU-T04	30	10	90	98
10	ZMU-T04	30	20	80	>99
11	ZMU-T04	30	40	63	>99
12	ZMU-T04	50	5	>99	>99
13	ZMU-T04	70	5	94	99

[a] Unless otherwise noted, mixtures of **1a**, cell suspension of *Pseudomonas monteilii* species, Na_2HPO_4-KH_2PO_4 buffer (100 mM, pH 7) in 5.0 mL reaction system were shaken at 250 rpm and 30 °C for 24 h.
[b] Determined by HPLC analysis.
[c] Determined by chiral HPLC analysis.
[d] LB medium was used.

Please cite this article in press as: Cui B, et al., Chemoenzymatic synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* species and sulfoxidation with chiral titanium complexe, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.07.014

Table 2
Scope of Asymmetric Reduction of β-Ketosulfides **1**.[a]

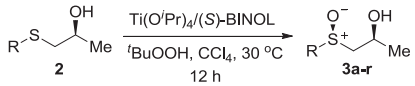


Entry	1	Conversion of 1[b] (%)	2/ee[c] (%)
1	R = 4-ClC$_6$H$_4$ (**1a**)	**2a**/>99	>99
2	R = Ph (**1b**)	**2b**/>99	97
3	R = 2-MeC$_6$H$_4$ (**1c**)	**2c**/96	>99
4	R = 2-EtC$_6$H$_4$ (**1d**)	**2d**/94	99
5	R = 2,4-Me$_2$C$_6$H$_3$ (**1e**)	**2e**/93	97
6	R = 2,5-Me$_2$C$_6$H$_3$ (**1f**)	**2f**/99	97
7	R = 2,4-F$_2$C$_6$H$_3$ (**1g**)	**2g**/99	>99
8	R = 2-ClC$_6$H$_4$ (**1h**)	**2h**/95	97
9	R = 2,3-Cl$_2$C$_6$H$_3$ (**1i**)	**2i**/79	>99
10	R = 2,4-Cl$_2$C$_6$H$_3$ (**1j**)	**2j**/92	97
11	R = 3-MeC$_6$H$_4$ (**1k**)	**2k**/>99	99
12	R = 4-MeC$_6$H$_4$ (**1l**)	**2l**/92	99
13	R = 3,5-Me$_2$C$_6$H$_3$ (**1m**)	**2m**/93	93
14	R = 3,4-F$_2$C$_6$H$_3$ (**1n**)	**2n**/>99	98
15	R = 3-ClC$_6$H$_4$ (**1o**)	**2o**/95	96
16	R = 3-BrC$_6$H$_4$ (**1p**)	**2p**/92	97
17	R = 4-BrC$_6$H$_4$ (**1q**)	**2q**/92	98
18	R = 2-naphthyl (**1r**)	**2r**/>99	92

[a] Unless otherwise noted, mixtures of **1** (5 mM), cell suspension of *Pseudomonas monteilii* species (50 cdw g/L), Na_2HPO_4-KH_2PO_4 buffer (100 mM, pH 7) in 5.0 mL reaction system were shaken at 250 rpm and 30 °C for 24 h.
[b] Determined by HPLC analysis.
[c] Determined by chiral HPLC analysis.

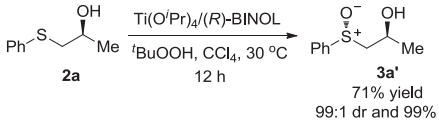
with 56:44 dr and 98% ee in the absence of (*S*)-BINOL, which revealed the chiral ligand played an important role in the stereocontrol, but the merely inherent chirality of hydroxyl in **2a** had no obvious steric induction in this oxidative transformation [Scheme 3, Eq. (a)]. Additionally, the chemo-enzymatic synthesis of β-hydroxyl-sulfoxide **3a** could also be achieved by exchanging the bioreduction of ketone and chemical oxidation of sulfide, but giving inferior total yield and slightly lower dr of **3a** [Scheme 3, Eq. (b)]. It was speculated that the function of free hydroxyl in **2a** may be necessary for the acceleration and stereocontrol of the oxidation process. In order to further confirm our speculation, the methyl protected intermediate **5** was employed into the asymmetric sulfoxidation. Not surprisingly, the product **6** was just obtained in 15% yield with 72:28 dr [Scheme 3, Eq. (c)].

Table 3
Scope of Asymmetric Sulfoxidation of β-Hydroxyl-Sulfides **2**.[a]



Entry	2	3/yield[b] (%)	dr[c]	ee[d] (%)
1	R = 4-ClC$_6$H$_4$ (**2a**)	**3a**/88	99:1	>99
2	R = Ph (**2b**)	**3b**/62	94:6	>99
3	R = 2-MeC$_6$H$_4$ (**2c**)	**3c**/66	87:13	99
4	R = 2-EtC$_6$H$_4$ (**2d**)	**3d**/64	81:19	>99
5	R = 2,4-Me$_2$C$_6$H$_3$ (**2e**)	**3e**/41	99:1	>99
6	R = 2,5-Me$_2$C$_6$H$_3$ (**2f**)	**3f**/70	76:24	>99
7	R = 2,4-F$_2$C$_6$H$_3$ (**2g**)	**3g**/70	79:21	>99
8	R = 2-ClC$_6$H$_4$ (**2h**)	**3h**/93	77:23	94
9	R = 2,3-Cl$_2$C$_6$H$_3$ (**2i**)	**3i**/98	88:12	>99
10	R = 2,4-Cl$_2$C$_6$H$_3$ (**2j**)	**3j**/90	76:24	98
11	R = 3-MeC$_6$H$_4$ (**2k**)	**3k**/38	98:2	>99
12	R = 4-MeC$_6$H$_4$ (**2l**)	**3l**/44	90:10	>99
13	R = 3,5-Me$_2$C$_6$H$_3$ (**2m**)	**3m**/34	96:4	97
14	R = 3,4-F$_2$C$_6$H$_3$ (**2n**)	**3n**/51	90:10	>99
15	R = 3-ClC$_6$H$_4$ (**2o**)	**3o**/41	92:8	99
16	R = 3-BrC$_6$H$_4$ (**2p**)	**3p**/59	96:4	>99
17	R = 4-BrC$_6$H$_4$ (**2q**)	**3q**/64	99:1	>99
18	R = 2-naphthyl (**2r**)	**3r**/91	84:16	>99

[a] Unless otherwise noted, all reactions were performed with substrates **2** (0.25 mmol), Ti(O^{i}Pr)$_4$ (0.025 mmol), (*S*)-BINOL (0.05 mmol), H_2O (4.5 μL, 0.25 mmol) and ^{t}BuOOH (70% of aqueous solution, 0.5 mmol) in 5.0 mL of CCl_4 at 30 °C for 12 h.
[b] Isolated yields of **3**.
[c] Determined by chiral HPLC analysis.
[d] Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis.



Scheme 2. Asymmetric synthesis of another diastereomer **3a'**.

On the basis of the above control experiments and the previous literature report,[12] a plausible chelate structure of the titanium complexe in the asymmetric sulfoxidation of β-hydroxyl-sulfides **2** was proposed in Scheme 4. Firstly, Ti(O^{i}Pr)$_4$ coordinated with (*S*)-BINOL via the ligand exchange. In addition, the hydroxyl group and sulfur atom of β-hydroxyl-sulfides **2** might also combine with the titanium centre to form the chelate transition structure. Finally, the asymmetric sulfoxidation with ^{t}BuOOH gave the β-hydroxyl-sulfoxides **3**.

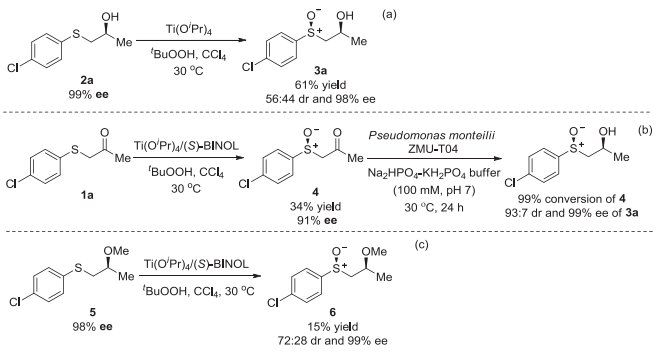
3. Conclusion

In summary, we have developed an efficient complementary methodology for the stereoselective synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* ZMU-T04 and sulfoxidation with Ti(O^{i}Pr)$_4$/(*S*)-BINOL complexe. Under the mild reaction conditions, a wide range of β-hydroxyl-sulfoxide derivatives were smoothly synthesized from the starting β-ketosulfides with excellent stereoselectivities (up to 99:1 dr and >99% ee). Moreover, a plausible chelate titanium complexe for the asymmetric sulfoxidation of β-hydroxyl-sulfide was presented.

4. Experimental section

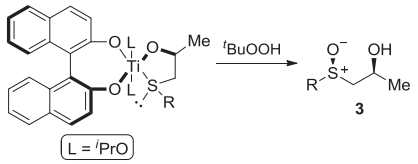
4.1. General methods

Reagents were purchased from commercial sources and were directly used unless otherwise noted. ^{1}H NMR and ^{13}C NMR (400 and 100 MHz, respectively) spectra were recorded in $CDCl_3$. ^{1}H



Scheme 3. Control experiments.

Please cite this article in press as: Cui B, et al., Chemoenzymatic synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* species and sulfoxidation with chiral titanium complexe, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.07.014



Scheme 4. Speculated structure of titanium complexe in the asymmetric sulfoxidation of β-hydroxyl-sulfides **2**.

NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm). Data were reported as the follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet and m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts were reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.16 ppm).

4.2. Process for the strain cultivation

The cells of *Pseudomonas monteilii* strain were transferred from M9 agar plate into 10 mL LB medium (10 g tryptone, 5 g yeast extract and 5 g NaCl in 1 L deionized water), and the mixture was shaken at 30 °C and 250 rpm for 8 h. Then 1 mL of solution collected from the above mixture was added into 50 mL M9 liquid medium (17.09 g $NaHPO_4·12H_2O$, 3.00 g KH_2PO_4, 0.50 g NaCl, 1.00 g NH_4Cl in 1000 mL deionized water) containing trace elements [HCl (1 mol/L), $FeSO_4·7H_2O$ (4.87 g/L), $CaCl_2·2H_2O$ (4.12 g/L), $MnCl_2·4H_2O$ (1.50 g/L), $ZnSO_4$ (1.05 g/L), H_3BO_3 (0.3 g/L), $Na_2MoO_4·2H_2O$ (0.25 g/L), $CuCl_2·2H_2O$ (0.15 g/L), $Na_2EDTA·2H_2O$ (0.84 g/L)] 50 μL, Mg_2SO_4 (1 mol/L) 100 μL and toluene 50 μL in a 250 mL shaking flask to adjust the initial cell concentration to 0.1 g cdw/L (cell dry weight/L). 15 mL of plastic tube with 500 μL of toluene was put into the flask and the vapor of toluene was used as carbon source. The mixture was incubated at 30 °C and 250 rpm for 24 h. After incubation, the bacterium cells were harvested by centrifugation and used for the following biotransformation.

4.3. General procedure for the asymmetric reduction of β-ketosulfides **1**

Whole cells of *Pseudomonas monteilii* ZMU-T04 (50 g cdw/L) was resuspended in 5 mL phosphate buffer (50 mM Na_2HPO_4/KH_2PO_4, pH 7). Then the solution of β-ketosulfides **1** (0.025 mmol, 5 mM) in 100 μL of EtOH was added into the above solution and the mixture was shaken at 30 °C and 250 rpm for 24 h. After completion of the reaction, the mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1). It was noted that 30 parallel experiments were performed for collecting the pure compounds **2**.

4.4. General procedure for the asymmetric sulfoxidation of β-hydroxyl-sulfides **2**

The mixture with β-hydroxyl-sulfides **2** (0.25 mmol), $Ti(O^iPr)_4$ (0.025 mmol), (*S*)-BINOL (0.05 mmol), H_2O (4.5 μL, 0.25 mmol) and ^{t}BuOOH (70% of aqueous solution, 0.5 mmol) in 5.0 mL of CCl_4 was stirred at 30 °C for 12 h. After completion of the reaction, the solvent was removed in vacuo and the residue was directly purified by column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to give the title products **3**.

4.4.1. (*S*)-1-((*S*)-(4-chlorophenyl)sulfinyl)propan-2-ol (**3a**)

Yellow oil; 88% yield; 99:1 dr, >99% ee, $[\alpha]_D^{25} = -164.7$ (*c* 0.97, $CHCl_3$). The ee was determined by HPLC analysis (Chiralcel OJ-H, ^{i}PrOH/hexane = 5/95, flow rate 0.8 mL/min, λ = 254 nm, t_{major} = 19.1 min). ^1H NMR (300 MHz, $CDCl_3$) δ (major) 7.61–7.58 (m, 2H), 7.53–7.51 (m, 2H), 4.49–4.45 (m, 1H), 3.63 (s, 1H), 2.97 (dd, *J* = 9.0 Hz, 13.1 Hz, 1H), 2.78 (dd, *J* = 2.7 Hz, 13.1 Hz, 1H), 1.32 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 142.4, 137.8, 129.9, 125.4, 65.2, 63.9, 23.4. HRMS (ESI-TOF): calcd for $C_9H_{11}ClNaO_2S$ $[M + Na]^+$: 241.0060; found: 241.0070.

4.4.2. (*S*)-1-((*S*)-phenylsulfinyl)propan-2-ol (**3b**)

Yellow solid; 62% yield; 94:6 dr, >99% ee, $[\alpha]_D^{25} = -320.8$ (*c* 0.61, $CHCl_3$); mp 62.8–64.1 °C. The ee was determined by HPLC analysis (Chiralcel OD, ^{i}PrOH/hexane = 10/90, flow rate 0.7 mL/min, λ = 254 nm, t_{major} = 24.8 min). ^1H NMR (300 MHz, $CDCl_3$) δ (major) 7.67–7.64 (m, 2H), 7.55–7.53 (m, 3H), 4.53–4.48 (m, 1H), 3.81 (s, 1H), 2.98 (dd, *J* = 9.1 Hz, 13.1 Hz, 1H), 2.78 (dd, *J* = 2.6 Hz, 13.1 Hz, 1H), 1.31 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 144.0, 131.6, 129.6, 124.0, 65.3, 63.8, 23.4. HRMS (ESI-TOF): calcd for $C_9H_{12}NaO_2S$ $[M + Na]^+$: 207.0450; found: 207.0456.

4.4.3. (*S*)-1-((*S*)-o-tolylsulfinylpropan-2-ol (**3c**)

Pale yellow solid; 66% yield; 87:13 dr, 99% ee, $[\alpha]_D^{25} = -144.1$ (*c* 0.62, $CHCl_3$); mp 65.8–67.2 °C. The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 28.9 min, t_{major} = 35.9 min). ^1H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.92–7.88 (m, 1H), 7.44–7.35 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 4.49–4.37 (m, 1.4H), 4.18 (s, 0.6H), 2.97 (dd, *J* = 9.9 Hz, 13.4 Hz, 0.4H), 2.78–2.90 (m, 1.6H), 2.34 (d, *J* = 8.9 Hz, 3H), 1.31 (d, *J* = 6.3 Hz, 2H), 1.24 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 142.0, 140.9, 134.4, 134.2, 131.1, 130.9, 130.8, 127.6, 127.3, 123.9, 123.6, 65.1, 62.6, 62.0, 61.2, 23.3, 23.2, 18.2, 18.1. HRMS (ESI-TOF): calcd for $C_{10}H_{14}NaO_2S$ $[M + Na]^+$: 221.0607; found: 221.0605.

4.4.4. (*S*)-1-((*S*)-2-ethylphenylsulfinylpropan-2-ol (**3d**)

Yellow oil; 64% yield; 81:19 dr, >99% ee, $[\alpha]_D^{25} = -182.2$ (*c* 0.89, $CHCl_3$). The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 5/95, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 42.3 min). ^1H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.96–7.94 (m, 1H), 7.45–7.43 (m, 2H), 7.26–7.25 (m, 1H), 4.52–4.49 (m, 0.7H), 4.43–4.39 (m, 0.3H), 4.20 (s, 0.3H), 4.12 (s, 0.7H), 2.99–2.80 (m, 2H), 2.78–2.60 (m, 3H), 1.32–1.30 (m, 2H), 1.28–1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 141.7, 140.8, 140.6, 140.4, 131.5, 131.3, 129.0, 128.9, 127.8, 127.4, 124.1, 123.8, 65.4, 62.9, 62.7, 61.9, 24.8, 24.6, 23.4, 23.3, 15.4, 15.1. HRMS (ESI-TOF): calcd for $C_{11}H_{16}NaO_2S$ $[M + Na]^+$: 235.0763; found: 235.0755.

4.4.5. (*S*)-1-((*S*)-(2,4-dimethylphenyl)sulfinylpropan-2-ol (**3e**)

Pale yellow solid; 41% yield; 99:1 dr, >99% ee, $[\alpha]_D^{25} = -127.2$ (*c* 0.62, $CHCl_3$); mp 166.1–167.0 °C. The ee was determined by HPLC analysis (Chiralcel OJ-H, ^{i}PrOH/hexane = 5/95, flow rate 0.8 mL/min, λ = 254 nm, t_{major} = 13.0 min). ^1H NMR (400 MHz, $CDCl_3$) δ (major) 7.80 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.02 (s, 1H), 4.52 (s, 1H), 4.03 (s, 1H), 2.86–2.77 (m, 2H), 2.37 (s, 3H), 2.33 (s, 3H), 1.31 (d, *J* = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 141.7, 138.9, 134.3, 131.6, 128.5, 123.8, 65.5, 61.6, 23.4, 21.4, 18.2. HRMS (ESI-TOF): calcd for $C_{11}H_{16}NaO_2S$ $[M + Na]^+$: 235.0763; found: 235.0761.

4.4.6. (*S*)-1-((*S*)-(2,5-dimethylphenyl)sulfinylpropan-2-ol (**3f**)

Yellow solid; 70% yield; 76:24 dr, >99% ee, $[\alpha]_D^{25} = -178.9$ (*c* 0.88, $CHCl_3$); mp 83.6–85.5 °C. The ee was determined by HPLC analysis (Chiralpak IA-3, ^{i}PrOH/hexane = 5/95, flow rate 0.8 mL/min,

Please cite this article in press as: Cui B, et al., Chemoenzymatic synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* species and sulfoxidation with chiral titanium complexe, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.07.014

λ = 254 nm, t_{major} = 21.7 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.73 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.11–7.08 (m, 1H), 4.57–4.50 (m, 0.7H), 4.43–4.36 (m, 0.3H), 4.13–4.08 (m, 1H), 3.06–3.00 (m, 0.4H), 2.87–2.77 (m, 1.6H), 2.40 (d, J = 5.2 Hz, 3H), 2.30 (d, J = 10.8 Hz, 3H), 1.31 (d, J = 6.3 Hz, 2H), 1.25 (d, J = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 141.6, 140.1, 137.8, 137.3, 132.1, 131.9, 131.1, 131.0, 130.9, 130.8, 124.3, 123.7, 65.5, 63.1, 61.3, 59.7, 23.4, 23.3, 21.2, 21.1, 17.8, 17.7. HRMS (ESI-TOF): calcd for $C_{11}H_{16}NaO_2S$ $[M + Na]^+$: 235.0763; found: 235.0764.

4.4.7. (S)-1-((S)-(2,4-difluorophenyl)sulfinylpropan-2-ol (**3g**)

Pale yellow solid; 70% yield; 79:21 dr, >99% ee, $[\alpha]_D^{25} = -130.4$ (c 0.66, $CHCl_3$); mp 83.1–84.5 °C. The ee was determined by HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane = 8/92, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 36.1 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.86–7.81 (m, 1H), 7.17–7.13 (m, 1H), 6.93–6.88 (m, 1H), 4.59–4.55 (m, 0.8H), 4.32 (s, 0.2H), 3.67 (s, 0.2H), 3.48 (s, 0.8H), 3.26–3.21 (m, 0.2H), 3.07–3.03 (m, 0.8H), 2.98–2.92 (m, 0.8H), 2.76 (d, J = 13.7 Hz, 0.2H), 1.35 (d, J = 6.4 Hz, 2.4H), 1.27–1.25 (m, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 165.2 (d, J = 253.0 Hz, 1C), 165.1 (d, J = 253.2 Hz, 1C), 157.9 (d, J = 248.5 Hz, 1C), 157.8 (d, J = 248.5 Hz, 1C), 128.0 (dd, J = 4.0 Hz, 10.0 Hz, 1C), 127.2 (dd, J = 3.9 Hz, 10.2 Hz, 1C), 113.3 (dd, J = 3.4 Hz, 21.9 Hz), 105.0, 104.9 (d, J = 50.1 Hz, 1C), 104.8 (d, J = 50.2 Hz, 1C), 104.7, 65.0, 63.5, 61.8, 59.8, 23.4, 23.3. HRMS (ESI-TOF): calcd for $C_9H_{10}F_2NaO_2S$ $[M + Na]^+$: 243.0262; found: 243.0252.

4.4.8. (S)-1-((S)-(2-chlorophenyl)sulfinyl)propan-2-ol (**3h**)

White solid; 93% yield; 77:23 dr, 94% ee, $[\alpha]_D^{25} = -153.3$ (c 0.80, $CHCl_3$); mp 108.1–109.9 °C. The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 8/92, flow rate 0.8 mL/min, λ = 254 nm, t_{minor} = 22.0 min, t_{major} = 25.5 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.97–7.92 (m, 1H), 7.58–7.52 (m, 1H), 7.49–7.39 (m, 2H), 4.63–4.57 (m, 0.7H), 4.33–4.30 (m, 0.3H), 3.97 (s, 0.3H), 3.76 (s, 0.7H), 3.30 (dd, J = 9.6 Hz, 13.6 Hz, 0.3H), 3.22 (dd, J = 2.2 Hz, 13.2 Hz, 0.7H), 2.81 (dd, J = 8.3 Hz, 13.2 Hz, 1H), 1.34 (d, J = 6.4 Hz, 2H), 1.24 (d, J = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 142.0, 140.2, 135.2, 132.4, 131.0, 130.2, 130.0, 129.8, 128.4, 128.1, 126.7, 125.6, 65.4, 63.6, 60.6, 58.1, 23.3, 22.8. HRMS (ESI-TOF): calcd for $C_9H_{11}ClNaO_2S$ $[M + Na]^+$: 241.0060; found: 241.0058.

4.4.9. (S)-1-((S)-(2,3-dichlorophenyl)sulfinylpropan-2-ol (**3i**)

Brown solid; 98% yield; 88:12 dr, >99% ee, $[\alpha]_D^{25} = -145.1$ (c 1.03, $CHCl_3$); mp 77.7–79.4 °C. The ee was determined by HPLC analysis (Chiralcel OJ-H, ^{i}PrOH/hexane = 5/95, flow rate 0.8 mL/min, λ = 254 nm, t_{major} = 17.1 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.85–7.82 (m, 1H), 7.62–7.59 (m, 1H), 7.52–7.47 (m, 1H), 4.59 (s, 0.8H), 4.33 (s, 0.2H), 3.88 (d, J = 25.4 Hz, 0.2H), 3.67 (d, J = 11.6 Hz, 0.8H), 3.33–3.22 (m, 1H), 2.84–2.76 (m, 1H), 1.36–1.33 (m, 2.4H), 1.27–1.25 (m, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 144.5, 134.0, 133.8, 132.8, 132.7, 132.7, 128.9, 128.6, 128.0, 127.8, 124.8, 123.9, 65.2, 63.3, 60.6, 58.8, 23.3. HRMS (ESI-TOF): calcd for $C_9H_{10}Cl_2NaO_2S$ $[M + Na]^+$: 274.9671; found: 274.9670.

4.4.10. (S)-1-((S)-(2,4-dichlorophenyl)sulfinylpropan-2-ol (**3j**)

White solid; 90% yield; 76:24 dr, 98% ee, $[\alpha]_D^{25} = -154.9$ (c 1.00, $CHCl_3$); mp 210.4–211.8 °C. The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 8/92, flow rate 0.8 mL/min, λ = 254 nm, t_{minor} = 16.4 min, t_{major} = 15.7 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.90–7.85 (m, 1H), 7.54–7.51 (m, 1H), 7.44–7.42 (m, 1H), 4.59–4.57 (m, 0.7H), 4.32 (s, 0.3H), 3.82 (s, 0.3H), 3.62 (s, 0.7H), 3.28 (dd, J = 9.8 Hz, 13.7 Hz, 0.3H), 3.19 (dd, J = 2.8 Hz, 13.2 Hz, 0.7H), 2.84–2.75 (m, 1H), 1.34 (d, J = 6.3 Hz, 2H), 1.25 (d, J = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 140.7, 139.1, 138.1, 138.0, 130.6, 130.4, 130.1, 129.9, 128.8, 128.6, 127.8, 126.9, 65.2, 63.4, 60.8, 58.7, 23.4. HRMS (ESI-TOF): calcd for $C_9H_{10}Cl_2NaO_2S$ $[M + Na]^+$: 274.9671; found: 274.9672.

4.4.11. (S)-1-((S)-m-tolylsulfinylpropan-2-ol (**3k**)

Yellow oil; 38% yield; 98:2 dr, >99% ee, $[\alpha]_D^{25} = -168.8$ (c 0.77, $CHCl_3$). The ee was determined by HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 14.6 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major) 7.48 (s, 1H), 7.40 (d, J = 4.3 Hz, 2H), 7.32–7.31 (m, 1H), 4.51–4.47 (m, 1H), 3.90 (s, 1H), 2.97 (dd, J = 9.2 Hz, 13.2 Hz, 1H), 2.76 (dd, J = 2.0 Hz, 13.2 Hz, 1H), 2.42 (s, 3H), 1.30 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 143.6, 139.9, 132.4, 129.4, 124.2, 121.1, 65.3, 63.7, 23.4, 21.6. HRMS (ESI-TOF): calcd for $C_{10}H_{14}NaO_2S$ $[M + Na]^+$: 221.0607; found: 221.0604.

4.4.12. (S)-1-((S)-p-tolylsulfinylpropan-2-ol (**3l**)

Yellow oil; 44% yield; 90:10 dr, >99% ee, $[\alpha]_D^{25} = -207.5$ (c 0.90, $CHCl_3$). The ee was determined by HPLC analysis (Chiralcel OJ-H, ^{i}PrOH/hexane = 10/90, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 14.8 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 7.54 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.53–4.49 (m, 1H), 3.82 (s, 1H), 2.95 (dd, J = 9.3 Hz, 13.1 Hz, 1H), 2.75 (dd, J = 2.3 Hz, 13.1 Hz, 1H), 2.42 (s, 3H), 1.30 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 142.2, 140.7, 130.3, 124.0, 65.4, 63.6, 23.5, 21.6. HRMS (ESI-TOF): calcd for $C_{10}H_{14}NaO_2S$ $[M + Na]^+$: 221.0607; found: 221.0614.

4.4.13. (S)-1-((S)-(3,5-dimethylphenyl)sulfinylpropan-2-ol (**3m**)

Yellow oil; 34% yield; 96:4 dr, 97% ee, $[\alpha]_D^{25} = -182.2$ (c 0.90, $CHCl_3$). The ee was determined by HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 12.5 min, t_{major} = 10.5 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major) 7.24 (s, 2H), 7.12 (s, 1H), 4.52–4.48 (m, 1H), 3.91 (s, 1H), 2.95 (dd, J = 9.2 Hz, 13.2 Hz, 1H), 2.75 (dd, J = 2.4 Hz, 13.2 Hz, 1H), 2.37 (s, 6H), 1.30 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 143.5, 139.7, 133.3, 121.3, 65.4, 63.6, 23.4, 21.4. HRMS (ESI-TOF): calcd for $C_{11}H_{16}NaO_2S$ $[M + Na]^+$: 235.0763; found: 235.0754.

4.4.14. (S)-1-((S)-(3,4-difluorophenyl)sulfinylpropan-2-ol (**3n**)

Yellow oil; 51% yield; 90:10 dr, >99% ee, $[\alpha]_D^{25} = -39.2$ (c 0.90, $CHCl_3$). The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 19.6 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major) 7.57–7.53 (m, 1H), 7.41–7.32 (m, 2H), 4.46–4.43 (m, 1H), 3.53 (s, 1H), 2.98 (dd, J = 8.9 Hz, 13.2 Hz, 1H), 2.79 (dd, J = 2.8 Hz, 13.2 Hz, 1H), 1.33 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 152.3 (dd, J = 12.5 Hz, 252.9 Hz, 1C), 151.2 (dd, J = 13.7 Hz, 253.8 Hz, 1C), 140.4, 120.7, 118.7 (d, J = 18.4 Hz, 1C), 113.8 (d, J = 19.4 Hz), 64.7, 64.5, 23.4. HRMS (ESI-TOF): calcd for $C_9H_{10}F_2NaO_2S$ $[M + Na]^+$: 243.0262; found: 243.0256.

4.4.15. (S)-1-((S)-3-chlorophenylsulfinylpropan-2-ol (**3o**)

Yellow oil; 41% yield; 92:8 dr, 99% ee, $[\alpha]_D^{25} = -119.7$ (c 1.27, $CHCl_3$). The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 15.6 min, t_{major} = 21.1 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major) 7.66 (s, 1H), 7.49–7.47 (m, 3H), 4.48–4.45 (m, 1H), 3.67 (s, 1H), 2.99 (dd, J = 8.8 Hz, 13.2 Hz, 1H), 2.81 (dd, J = 2.6 Hz, 13.2 Hz, 1H), 1.32 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 145.9, 136.0, 131.7, 130.8, 124.0, 122.0, 65.1, 64.0, 23.4. HRMS (ESI-TOF): calcd for $C_9H_{11}ClNaO_2S$ $[M + Na]^+$: 241.0060; found: 241.0054.

Please cite this article in press as: Cui B, et al., Chemoenzymatic synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* species and sulfoxidation with chiral titanium complexe, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.07.014

*4.4.16. (S)-1-((S)-3-bromophbbenylsulfinylpropan-2-ol (**3p**)*

Yellow oil; 59% yield; 96:4 dr, >99% ee, $[\alpha]_D^{25} = -122.9$ (*c* 0.90, $CHCl_3$). The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 48.3 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major) 7.80 (d, *J* = 1.6 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.42–7.40 (m, 1H), 4.46 (s, 1H), 3.68 (s, 1H), 3.02–2.96 (m, 1H), 2.82–2.78 (m, 1H), 1.33–1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 146.1, 134.6, 131.0, 126.8, 123.8, 122.5, 65.1, 64.0, 23.4. HRMS (ESI-TOF): calcd for $C_9H_{11}BrNaO_2S$ $[M + Na]^+$: 284.9555; found: 284.9550.

*4.4.17. (S)-1-((S)-4-bromophenylsulfinylpropan-2-ol (**3q**)*

Pale yellow solid; 64% yield; 99:1 dr, >99% ee, $[\alpha]_D^{25} = -173.5$ (*c* 1.01, $CHCl_3$); mp 107.3–108.5 °C. The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 25.6 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 7.70–7.67 (m, 2H), 7.54–7.51 (m, 2H), 4.50–4.45 (m, 1H), 3.61 (s, 1H), 2.96 (dd, *J* = 9.0 Hz, 13.1 Hz, 1H), 2.78 (dd, *J* = 2.6 Hz, 13.1 Hz, 1H), 1.32 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 143.1, 132.9, 126.0, 125.6, 65.2, 63.8, 23.5. HRMS (ESI-TOF): calcd for $C_9H_{11}BrNaO_2S$ $[M + Na]^+$: 284.9555; found: 284.9554.

*4.4.18. (S)-1-((S)-naphthalen-2-ylsulfinylpropan-2-ol (**3r**)*

Pale yellow solid; 91% yield; 84:16 dr, >99% ee, $[\alpha]_D^{25} = -80.7$ (*c* 1.05, $CHCl_3$); mp 132.1–133.9 °C. The ee was determined by HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 41.9 min, t_{major} = 49.4 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) 8.24 (s, 0.2H), 8.20 (s, 0.8H), 8.01–7.98 (m, 1H), 7.95–7.90 (m, 2H), 7.64–7.52 (m, 3H), 4.57–4.53 (m, 0.8H), 4.38 (m, 0.2H), 3.98 (s, 0.2H), 3.86 (s, 0.8H), 3.18 (dd, *J* = 9.8 Hz, 13.7 Hz, 0.2H), 3.05 (dd, *J* = 9.1 Hz, 13.2 Hz, 0.8H), 2.87 (dd, *J* = 1.8 Hz, 13.2, 0.8H), 2.72 (d, *J* = 13.6 Hz, 0.2H), 1.33 (d, *J* = 6.2 Hz, 2.4H), 1.23 (d, *J* = 6.4 Hz, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 140.8, 134.7, 133.0, 129.9, 129.7, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.6, 124.9, 124.7, 119.8, 119.7, 65.4, 63.5, 63.3, 23.5, 23.4. HRMS (ESI-TOF): calcd for $C_{13}H_{14}NaO_2S$ $[M + Na]^+$: 257.0607; found: 257.0604.

*4.5. Procedure for the sulfoxidation of **2a** to **3a** without (S)-BINOL*

To the mixture of $Ti(O^iPr)_4$ (7.5 μL, 0.025 mmol) and H_2O (4.5 μL, 0.25 mmol) in CCl_4 (3 mL) was added a solution of **2a** (99% ee, 50.7 mg, 0.25 mmol) in 2 mL of CCl_4. The resulting solution was stirred at 30 °C for 10 min, and then ^{t}BuOOH (70% aqueous solution, 70.6 μL, 0.5 mmol) was added and the mixture was subsequently stirred at 30 °C for 12 h. After completion of the reaction, the solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (EtOAc/petroleum ether = 1:2) to give the product **3a** in 61% yield with 56:44 dr and 98% ee.

*4.6. Procedure for the synthesis of product **3a** via the exchange of the bio-reduction of ketone and chemical oxidation of sulfide*

To the mixture of (*S*)-BINOL (14.3 mg, 0.05 mmol), $Ti(O^iPr)_4$ (7.5 μL, 0.025 mmol) and H_2O (4.5 μL, 0.25 mmol) in CCl_4 (3 mL) was added a solution of substrate **1a** (50.2 mg, 0.25 mmol) in 2 mL of CCl_4. The resulting solution was stirred at 30 °C for 10 min, and then ^{t}BuOOH (70% aqueous solution, 70.6 μL, 0.5 mmol) was added and the mixture was subsequently stirred at 30 °C for 12 h. After completion of the reaction, the solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (EtOAc/petroleum ether = 1:2) to give the intermediate **4** in 34% yield with 91% ee.

After that, whole cells of *Pseudomonas monteilii* ZMU-T04 (50 g cdw/L) was resuspended in 5 mL phosphate buffer (50 mM Na_2HPO_4/KH_2PO_4, pH 7). Then the solution of **4** (5.4 mg, 0.025 mmol, 5 mM) in 100 μL of EtOH was added into the above solution and the mixture was shaken at 30 °C and 250 rpm for 24 h. After completion of the reaction, the mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give product **3a** with 93:7 dr and 99% ee and 99% conversion of **4**. It was noted that the above extracted organic phase was used for chiral HPLC analysis and 30 parallel experiments were performed for collecting the pure compound **3a**.

*4.6.1. (S)-1-((4-chlorophenyl)sulfinyl)propan-2-one **4***

Pale yellow solid; 34% yield; 91% ee, $[\alpha]_D^{25} = -96.2$ (*c* 0.60, $CHCl_3$). The ee was determined by HPLC analysis (Chiralcel OJ-H, ^{i}PrOH/hexane = 5/95, flow rate 0.8 mL/min, λ = 254 nm, t_{minor} = 68.6 min, t_{major} = 54.3 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.58 (m, 2H), 7.53–7.50 (m, 2H), 3.88–3.80 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 141.4, 138.1, 129.9, 125.6, 68.6, 32.2.

*4.7. Procedure for the synthesis of compound **6***

To the mixture of (*S*)-BINOL (14.3 mg, 0.05 mmol), $Ti(O^iPr)_4$ (7.5 μL, 0.025 mmol) and H_2O (4.5 μL, 0.25 mmol) in CCl_4 (3 mL) was added a solution of **5** (50.2 mg, 0.25 mmol) in 2 mL of CCl_4. The resulting solution was stirred at 30 °C for 10 min, and then ^{t}BuOOH (70% aqueous solution, 70.6 μL, 0.5 mmol) was added and the mixture was subsequently stirred at 30 °C for 12 h. After completion of the reaction, the solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (EtOAc/petroleum ether = 1:2) to give the product **6** in 15% yield with 72:28 dr and 99% ee.

*4.7.1. (S)-(4-chlorophenyl)(2-methoxypropyl)sulfane **5***

Yellow solid; 88% yield; 98% ee, $[\alpha]_D^{25} = -10.5$ (*c* 1.00, $CHCl_3$). The ee was determined by HPLC analysis (Chiralpak AY-H, ^{i}PrOH/hexane = 5/95, flow rate 0.5 mL/min, λ = 254 nm, t_{minor} = 10.7 min, t_{major} = 10.1 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 3.48 (dd, *J* = 6.1 Hz, 12.1 Hz, 1H), 3.34 (s, 3H), 3.10 (dd, *J* = 5.8 Hz, 13.2 Hz, 1H), 2.90 (dd, *J* = 6.1 Hz, 13.1 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.1, 130.7, 129.1, 75.9, 56.7, 40.1, 19.0.

*4.7.2. 1-Chloro-4-((S)-((S)-2-methoxypropyl)sulfinyl)benzene **6***

Yellow solid; 15% yield; 72:28 dr, >99% ee, $[\alpha]_D^{25} = -22.9$ (*c* 0.75, $CHCl_3$). The ee was determined by HPLC analysis (Chiralcel OD-H, ^{i}PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 18.6 min, t_{major} = 16.7 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) 7.60–7.56 (m, 2H), 7.51–7.46 (m, 2H), 3.96–3.91 (m, 0.6H), 3.59–3.54 (m, 0.4H), 3.45–3.44 (m, 1.7H), 3.22–3.21 (m, 1.3H), 3.19–3.14 (m, 0.4H), 2.78–2.72 (m, 1.6H), 1.32–1.30 (m, 1.4H), 1.24–1.22 (m, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 143.3, 142.3, 137.4, 137.2, 129.7, 129.6, 125.7, 125.3, 71.7, 70.8, 66.4, 63.8, 56.9, 56.0, 19.0, 18.8.

Acknowledgments

We are grateful for financial support from National Nature Science Foundation of China (21262051), Science and Technology Department of Guizhou Province (QKHRCTD-2014-4002, QKHRC-2016-4029, QKHPTRC-2016-5801), and New Century Excellent Talent of the Ministry of Education (NCET-13-1069).

Please cite this article in press as: Cui B, et al., Chemoenzymatic synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* species and sulfoxidation with chiral titanium complexe, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.07.014

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.07.014.

References

1. For reviews, see: (a) Cheng D, Ishihara Y, Tan B, Barbas III CF. *ACS Catal*. 2014;4:743–762;
   (b) Gopalaiah K. *Chem Rev*. 2013;113:3248–3296;
   (c) Brenna E, Fuganti C, Gattiand FG, Serra S. *Chem Rev*. 2011;111:4036–4072.
2. For reviews, see: (a) Lee JM, Na Y, Han H, Chang S. *Chem Soc Rev*. 2004;33:302–312;
   (b) Wasilke J-C, Obrey SJ, Baker RT, Bazan GC. *Chem Rev*. 2005;105:1001–1020;
   (c) Pàmies O, Bäckval J-E. *Chem Rev*. 2003;103:3247–3261.
3. For selected examples, see: (a) Denard CA, Bartlett MJ, Wang Y, Lu L, Hartwig JF, Zhao H. *ACS Catal*. 2015;5:3817–3822;
   (b) Denard CA, Huang H, Bartlett MJ, et al. *Angew Chem Int Ed*. 2014;53:465–469;
   (c) Rulli G, Duangdee N, Baer K, Hummel W, Berkessel A, Gröger H. *Angew Chem Int Ed*. 2011;50:7944–7947;
   (d) Schnapperelle I, Hummel W, Gröger H. *Chem Eur J*. 2012;18:1073–1076;
   (e) Schrittwieser JH, Coccia F, Kara S, et al. *Green Chem*. 2013;15:3318–3331.
4. For selected examples, see: (a) Naka T, Minakawa N, Kaga D, Matsuda A. *J Am Chem Soc*. 2000;122:7233–7243;
   (b) Solladie G, Wilb N, Bauder C. *Tetrahedron Lett*. 2000;41:4189–4192;
   (c) Gruttadauria M, Meo P, Noto R. *Tetrahedron*. 1999;55:14097, 14088;
   (d) Gruttadauria M, Meo P, Noto R. *Tetrahedron*. 1999;55:4769–4782;
   (e) Carreño MC. *Chem Rev*. 1995;95:1717–1760.
5. (a) Singh S, Kumar S, Chimni SS. *Tetrahedron Asymmetry*. 2001;12:2457–2462;
   (b) Laumen K, Breitgoff D, Schneider MP. *J Chem Soc, Chem Commun*. 1988:1459–1461.
6. (a) Holland HL, Brown FM, Barrett F, French J, Johnson DV. *J Ind Microbiol Biotechnol*. 2003;30:292–301;
   (b) Holland HL, Ihasz N, Lounsber BJ. *Can J Chem*. 2002;80:640–642.
7. Cardellicchio C, Omar OH, Naso F, Capozzi MAM, Capitellic F, Bertolasi V. *Tetrahedron Asymmetry*. 2006;17:223–229.
8. (a) Colobert F, Obringer M, Solladié G. *Eur J Org Chem*. 2006:1455–1467;
   (b) Obringer M, Colobert F, Neugnot B, Solladié G. *Org Lett*. 2003;5:629–632.
9. Chen Q, Wang K, Yuan C. *New J Chem*. 2009;33:972–975.
10. (a) Zhu C, Chen X, Yang Z, Du X, Liu Y, Cui Y. *Chem Commun*. 2013;49:7120–7122;
    (b) Cardellicchio C, Omar O, Naso HF, Capozzi MAM, Capitellic F, Bertolasi V. *Tetrahedron Asymmetry*. 2006;17:223–229;
    (c) Komatsu N, Hashizume M, Sugita T, Uemura S. *J Org Chem*. 1993;58:4529–4533.
11. (a) Zhao J, Guan S, Zhou X, Han W, Cui B, Chen Y. *Tetrahedron*. 2016;72:3098–3104;
    (b) Chen Y, Zhuo J, Zheng D, Tian S, Li Z. *J Mol Catal B Enzym*. 2014;106:100–104;
    (c) Chen Y, Lie F, Li Z. *Adv Synth Catal*. 2009;351:2107–2112;
    (d) Lie F, Chen Y, Wang Z, Li Z. *Tetrahedron Asymmetry*. 2009;20:1206–1211.
12. Matsugi M, Fukuda N, Muguruma Y, Yamaguchi T, Minamikawa J-i, Otsuka S. *Tetrahedron*. 2001;57:2739–2744.

Please cite this article in press as: Cui B, et al., Chemoenzymatic synthesis of β-hydroxyl-sulfoxides by a two-step reaction of enzymatic reduction using *Pseudomonas monteilii* species and sulfoxidation with chiral titanium complexe, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.07.014