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# Bio-mediated oxidative resolution of racemic 2-substituted 1,2,3,4-tetrahydroquinolines

Lei Qin, Daijun Zheng, Baodong Cui, Nanwei Wan, Xiaojian Zhou, Yongzheng Chen *

*School of Pharmacy, Zunyi Medical University, Zunyi 563000, PR China*

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ABSTRACT

Whole cell of *Pseudomonas monteilii* ZMU-T01 strains mediated oxidative resolution of racemic 2-substituted 1,2,3,4-tetrahydroquinolines has been successfully described. A series of highly enantioselective 2-substituted 1,2,3,4-tetrahydroquinoline derivatives were obtained in up to 50% conversion and >99% ee.


Optically active 1,2,3,4-tetrahydroquinoline ring system is a very important structural motif in the pharmaceutical and agrochemical industries.[1] In particular, the chiral 2-substituted 1,2,3,4-tetrahydroquinoline derivatives widely exist in numerous biologically active natural products and pharmacologically relevant therapeutic agents (Fig. 1),[1,2] as well as are employed as the starting materials for preparation of novel chiral ligands.[3] Thus, numerous different methodologies for the construction of chiral 2-substituted 1,2,3,4-tetrahydroquinoline scaffold have been established.[4–6] Obviously, the latest literature investigation reveals that these synthetic methods mainly focus on the asymmetric hydrogenation of 2-substituted quinolines with metal catalysts[4], organocatalysts,[5] and tandem reactions.[6] However, almost all the methodologies reported to date require the participation of hazardous materials such as the toxic reagents or expensive metals. Accordingly, considerable effort is still being directed to the development of elegant and environmentally friendly methods for the synthesis of optically active 2-substituted 1,2,3,4-tetrahydroquinoline derivatives on account of their prevalence in the pharmaceutical molecules.

In recent years, biocatalysis has gradually become a greener and more universal method for the efficient and enantioselective synthesis due to their non-toxicity of biocatalysts and mild reaction conditions.[7] Especially, bio-mediated oxidative deracemization is often the method of choice for the preparation of enantiopure compounds. These advantages were displayed by the success of deracemization on amines[8,9] and alcohols.[10]

To the best of our knowledge, the enzyme catalyzed oxidative kinetic resolution for the synthesis of chiral 2-substituted 1,2,3,4-tetrahydroquinoline derivatives is still rare. Recently, Zhu and coworkers reported deracemization of 2-methyl-1,2,3,4-tetrahydroquinoline with flavin-dependent cyclohexylamine oxidase mutant leading to the production of (*R*)-2-methyl-1,2,3,4-tetrahydroquinoline with 76% yield and 98% ee.[9] In addition, the catalytic asymmetric oxidation of sulfides and 1,2,3,4-tetrahydroquinolines by the whole cell of *Pseudomonas monteilii* ZMU-T01 strains has been achieved in our laboratory.[11] Furthermore, it was found that this biocatalyst also showed excellent activity and enantioselectivity for the deracemization of 2-subsituted 1,2,3,4-tetrahydroquinolines, giving a series of desired chiral 2-subsituted 1,2,3,4-tetrahydroquinoline derivatives in up to 50% conversion and >99% ee. In view of the important applications of this kind of compounds in pharmaceutical field and our interest in the development of biocatalytic oxidation methodologies,[10e,11] herein, we wish to report our endeavors on this subject.

To optimize the reaction conditions, the bio-oxidative resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinoline **1a** was employed as a model reaction. We first examined our laboratory's different strains from *Pseudomonas. monteilii* (Table 1). The screening of strains from ZMU-T01 to ZMU-T19 revealed that ZMU-T01 strains showed acceptable results, giving (*R*)-**1a** with 60% ee and 38% conversion of (*rac*)-**1a** to 2-methyl-quinoline **2a** (Table 1, entry 1). Other strains, including ZMU-T02, ZMU-T04 and ZMU-T15, gave

* Corresponding author.

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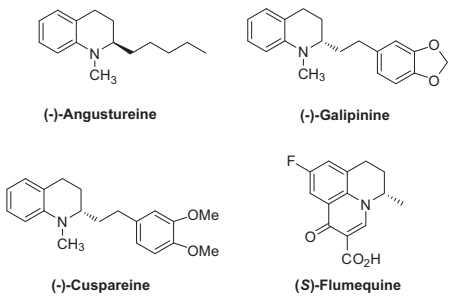


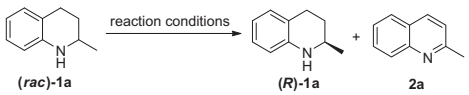

**Figure 1.** Selective examples of pharmacologically relevant therapeutic agents derived from chiral 2-substituted 1,2,3,4-tetrahydroquinolines.

lower enantioselectivities of (*R*)-**1a** (Table 1, entries 2–4). The ZMU-T18 and ZMU-T19 strains, by contrast, showed unsatisfactory resolution activities (Table 1, entries 5 and 6). The pH effect on the oxidative resolution of (*rac*)-**1a** was next evaluated. When the reaction was conducted under the weak acidic conditions (pH = 6), similar resolution results were obtained with that conducted at pH of 7 (Table 1, entry 1 vs. entry 7). Adjustment of the pH from 7 to 8 or 9 indicated that weak basic reaction conditions were beneficial for the oxidative resolution of (*rac*)-**1a**, and pH of 8 provided relatively high enantioselectivity of (*rac*)-**1a** (up to 69% ee) (Table 1, entry 8 vs. entries 1 and 9). In order to further improve the enantioselectivity of the oxidative resolution, cell concentration of *Pseudomonas monteilii* ZMU-T01 strains was also investigated. Unfortunately, both decrease and increase of the cell concentration could not furnish preferable resolution results (Table 1, entries 10 and 11). To our delight, increasing of the substrate concentration of (*rac*)-**1a** from 2 mM to 4 mM, the ee of (*R*)-**1a** could be significantly increased from 70% to 90%, and the conversion of (*rac*)-**1a** to 2-methyl-quinoline **2a** was also increased from 41% to 47% (Table 1, entry 12).

After establishment of reaction conditions (Table 1, entry 12), substrate scope of the whole cell of *Pseudomonas monteilii* ZMU-T01 strains mediated oxidative resolution of (*rac*)-2-substituted 1,2,3,4-tetrahydroquinolines **1** was following tested. As indicated in Table 2, both racemic substrates **1c** and **1d** containing the linear alkyl substituent (*n*-Pr and *n*-Bu) at C2 position could give the desired corresponding products (*R*)-**1c** and (*R*)-**1d** with high enantioselectivities (up to >99% ee) and 50% conversion of (*rac*)-**1c** to (*R*)-**2c** (Table 2, entries 3 and 4). Exceptionally, relatively low ee of (*R*)-**1b** was obtained when using (*rac*)-**1b** with ethyl group at the C2 position as the substrate (Table 2, entry 2). Besides, changing substituent at C2 position of (*rac*)-2-substituted 1,2,3,4-tetrahydroquinolines into the branched alkyl group (*i*-Pr and *i*-Bu) showed the excellent results as well (Table 2, entries 5 and 6). It is noteworthy that substrates **1g** and **1h** with unsaturated substituent (allyl and cyclopropyl) at C2 position also could be applied to the whole cell catalyzed resolution process, giving the corresponding products (*S*)-**1g** and (*S*)-**1h** with >99% ee and >99% ee, respectively (Table 2, entries 7 and 8). Unfortunately, (*R*)-**1i** and **1j** compounds were not obtained by using the racemic substrates **1i** and **1j** bearing a methyl or methoxy substitution on the phenyl ring of tetrahydroquinoline (Table 2, entries 9 and 10).

The practical application of the whole cell of *Pseudomonas monteilii* ZMU-T01 strain mediated oxidative resolution of (*rac*)-2-substituted 1,2,3,4-tetrahydroquinolines **1** could be illustrated by the transformation of resolution product (*R*)-**1c** into the antimalarial reagent **3**[1,2a] according to the literature reported method (Scheme 1).[12]

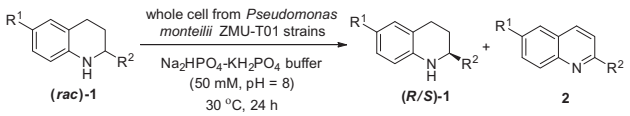
**Table 1**
Screening of reaction conditions[a]




| Entry | Strains | pH | Cell concentration (cdw g/L) | (*R*)-**1a**/ee[b,c] (%) | **2a**/*c*[d] (%) |
|---|---|---|---|---|---|
| 1 | *Pseudomonas monteilii* ZMU-T01 | 7 | 30 | 60 | 38 |
| 2 | *Pseudomonas monteilii* ZMU-T02 | 7 | 30 | 16 | 14 |
| 3 | *Pseudomonas monteilii* ZMU-T04 | 7 | 30 | 32 | 24 |
| 4 | *Pseudomonas monteilii* ZMU-T15 | 7 | 30 | 58 | 37 |
| 5 | *Pseudomonas monteilii* ZMU-T18 | 7 | 30 | 20 | 17 |
| 6 | *Pseudomonas monteilii* ZMU-T19 | 7 | 30 | 0 | 0 |
| 7 | *Pseudomonas monteilii* ZMU-T01 | 6 | 30 | 59 | 37 |
| 8 | *Pseudomonas monteilii* ZMU-T01 | 8 | 30 | 69 | 41 |
| 9 | *Pseudomonas monteilii* ZMU-T01 | 9 | 30 | 64 | 39 |
| 10 | *Pseudomonas monteilii* ZMU-T01 | 8 | 10 | 22 | 18 |
| 11 | *Pseudomonas monteilii* ZMU-T01 | 8 | 50 | 70 | 41 |
| 12 | *Pseudomonas monteilii* ZMU-T01 | 8 | 50 | 90[e] | 47 |

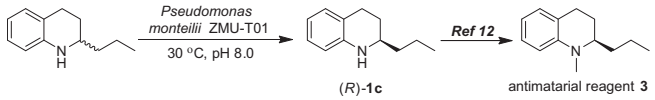
[a] Unless otherwise noted, mixtures of (*rac*)-**1a** (2 mM), cell suspension, $Na_2HPO_4$–$KH_2PO_4$ buffer (50 mM) in 5.0 mL reaction system were shaken at 250 rpm and 30 °C for 24 h.
[b] Determined by chiral HPLC analysis.
[c] The absolute configuration of the chiral product was assigned by comparison of the specific optical rotation with literature report.[4b]
[d] Conversion of (*rac*)-**1a** to **2a**: $c = [(R)\text{-}\mathbf{1a}/\text{ee}]/[1 + (R)\text{-}\mathbf{1a}/\text{ee}]$. The conversion was determined with the premise that no other side reaction was detected.
[e] 4 mM of (*rac*)-**1a** was used.

**Table 2**
Substrate scope for the bio-mediated oxidative resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinolines **1**[a]




| Entry | (*rac*)-**1** | (*R*/*S*)-**1**/ee[b,c] (%) | **2**/*c*[d] (%) |
|---|---|---|---|
| 1 | $R^1$ = H, $R^2$ = Me (**1a**) | (*R*)-**1a**/90[e] | **2a**/47 |
| 2 | $R^1$ = H, $R^2$ = Et (**1b**) | (*R*)-**1b**/89[f] | **2b**/47 |
| 3 | $R^1$ = H, $R^2$ = *n*-Pr (**1c**) | (*R*)-**1c**/>99 | **2c**/50 |
| 4 | $R^1$ = H, $R^2$ = *n*-Bu (**1d**) | (*R*)-**1d**/95[g] | **2d**/49 |
| 5 | $R^1$ = H, $R^2$ = *i*-Pr (**1e**) | (*S*)-**1e**/>99[h] | **2e**/50 |
| 6 | $R^1$ = H, $R^2$ = *i*-Bu (**1f**) | (*S*)-**1f**/>99 | **2f**/50 |
| 7 | $R^1$ = H, $R^2$ = allyl (**1g**) | (*S*)-**1g**/>99[g] | **2g**/50 |
| 8 | $R^1$ = H, $R^2$ = cyclopropyl (**1h**) | (*S*)-**1h**/>99[g] | **2h**/50 |
| 9 | $R^1$ = Me, $R^2$ = Me (**1i**) | (*R*)-**1i**/0 | **2i**/trace |
| 10 | $R^1$ = OMe, $R^2$ = Me (**1j**) | (*R*)-**1j**/0 | **2j**/trace |

[a] Unless otherwise noted, mixtures of (*rac*)-**1** (2 mM), cell suspension (50 cdw g/L), $Na_2HPO_4$–$KH_2PO_4$ buffer (50 mM, pH = 8.0) in 5.0 mL reaction system were shaken at 250 rpm at 30 °C for 24 h.
[b] Determined by chiral HPLC analysis.
[c] The absolute configuration of the chiral products were assigned by comparison of the specific optical rotation with literature report.[4b]
[d] Conversion of (*rac*)-**1** to **2**: $c = [(R/S)\text{-}\mathbf{1}/\text{ee}]/[1 + (R/S)\text{-}\mathbf{1}/\text{ee}]$. The conversion was determined with the premise that ee value was high and no other side reaction was detected.
[e] 4 mM (*rac*)-**1a** was used.
[f] 4 mM (*rac*)-**1b** was used.
[g] pH = 9.0.
[h] pH = 7.0.




**Scheme 1.** Practical application of this oxidative resolution.

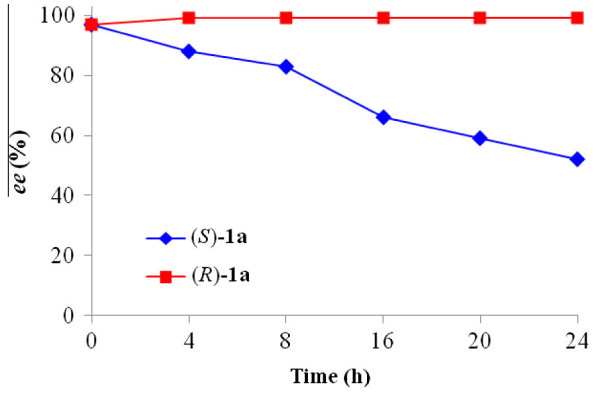
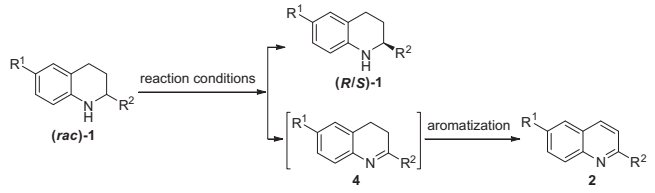



**Figure 2.** Changing curves of ee with time in the bio-mediated oxidative resolution of (*S*/*R*)-**1a**.




**Scheme 2.** Proposed mechanism of the bio-mediated oxidative resolution.

To investigate the mechanism of the bio-mediated oxidative resolution process, two controlled experiments were conducted and the changing curves of ee with time in the bio-meditated oxidative resolution of (*S*/*R*)-**1a** were also drawn (Fig. 2). It was found that the ee of (*S*)-**1a** was reduced gradually using 97% ee of (*S*)-**1a** as starting material, but the ee of (*R*)-**1a** was contrarily increased using 97% ee of (*R*)-**1a** substrate. Based on the controlled experiment results and the previous reports,[9,13] a possible mechanism of this bio-mediated oxidative resolution of (*rac*)-**1** to the corresponding single isomer (*S*/*R*)-**1** and quinolines **2** was proposed (Scheme 2). Under the optimal reaction conditions, one isomer (*S*/*R*)-**1** of (*rac*)-**1** was selectively oxidized to 3,4-dihydroquinoline **4** and followed by aromatization to produce quinoline **2a**, and the other single isomer (*R*/*S*)-**1** reserved therein.

In conclusion, we have developed an efficient and environmentally friendly bio-oxidative resolution process of (*rac*)-2-substituted 1,2,3,4-tetrahydroquinolines. Using the whole cell of *Pseudomonas monteilii* ZMU-T01 strains as biocatalyst, a series of (*rac*)-2-substituted 1,2,3,4-tetrahydroquinolines could be smoothly obtained with excellent enantioselectivities (up to >99% ee). The practical application of this oxidative resolution could be illustrated by the transformation of product (*R*)-**1c** into the antimalarial compound **3**. More detailed information on monoamine oxidase from *Pseudomonas monteilii* ZMU-T01 is essential and further studies are in progress.

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## Supplementary data

Supplementary data (general experimental procedures and $^{1}H$, $^{13}C$ NMR and HPLC for the chiral compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.066.

## References and notes

1. Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157–7259.
2. For selected examples, see: (a) Jacquemond-Collet, I.; Benoit-Vical, F.; Mustofa; Valentin, A.; Stanislas, E.; Mallié, M.; Fourasté, I. *Planta Med.* **2002**, *68*, 68–69; (b) Di Fabio, R.; Alvaro, G.; Bertani, B.; Donati, D.; Pizzi, D. M.; Gentile, G.; Pentassuglia, G.; Giacobbe, S.; Spada, S.; Ratti, E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1176–1180; (c) Rano, T. A.; Kuo, G.-H. *Org. Lett.* **2009**, *11*, 2812–2815; (d) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Combust. Sci.* **2011**, *13*, 65–71; (e) Tummatorn, J.; Muñoz, G. D.; Dudley, G. B. *Tetrahedron Lett.* **2013**, *54*, 1312–1314.
3. (a) Kannenberg, A.; Rost, D.; Eibauer, S.; Tiede, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3299–3302; (b) Liu, W. B.; Zheng, C.; Zhuo, C. X.; Dai, L. X.; You, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 4812–4821.
4. For selected examples, see: (a) Yang, P.-Y.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2004**, *15*, 1145–1149; (b) Wang, Z.-J.; Zhou, H.-F.; Wang, T.-L.; He, Y.-M.; Fan, Q.-H. *Green Chem.* **2009**, *11*, 767–769; (c) Wang, X.-B.; Zhou, Y.-G. *J. Org. Chem.* **2008**, *73*, 5640–5642; (d) Wang, C.; Li, C.; Wu, X.; Pettman, A.; Xiao, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524–6528; (e) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891; (f) Rueping, M.; Koenigs, R. M. *Chem. Commun.* **2011**, 304–306; (g) Tu, X.-F.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 11346–11349.
5. (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683–3686; (b) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759–762; (c) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852–865; (d) Shugrue, C. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 11173–11176.
6. (a) Patil, N. T.; Raut, V. S.; Tella, R. B. *Chem. Commun.* **2013**, 570–572; (b) Du, Y.-L.; Hu, Y.; Zhu, Y.-F.; Tu, X.-F.; Han, Z.-Y.; Gong, L.-Z. *J. Org. Chem.* **2015**, *80*, 4754–4759.
7. For reviews, see: (a) Patel, R. N. *Coord. Chem. Rev.* **2008**, *252*, 659–701; (b) Ni, Y.; Xu, J. H. *Biotechnol. Adv.* **2011**, *30*, 1279–1288; (c) Bornscheuer, U.; Huisman, G.; Kazlauskas, R.; Lutz, S.; Moore, J.; Robins, K. *Nature* **2012**, *485*, 185–194.
8. For reviews, see: (a) Gotor-Fernández, V.; Busto, E.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 797–812; (b) Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647–658.
9. Li, G.; Ren, J.; Yao, P.; Duan, Y.; Zhang, H.; Wu, Q.; Feng, J.; Lau, P. C. K.; Zhu, D. *ACS Catal.* **2014**, *4*, 903–908.
10. (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354; (b) Martin-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825; (c) Bogár, K.; Vidal, P. H.; Alcántara León, A. R.; Bäckvall, J. E. *Org. Lett.* **2007**, *9*, 3401–3404; (d) Hapău, D.; Brem, J.; Zaharia, V. *Tetrahedron: Asymmetry* **2011**, *22*, 2165–2171; (e) Zhou, X.; Zheng, D.; Cui, B.; Han, W.; Chen, Y. *Tetrahedron* **2015**, *71*, 4738–4744.
11. (a) Zheng, D.; Yang, M.; Zhuo, J.; Li, K.; Zhang, H.; Yang, J.; Cui, B.; Chen, Y. *J. Mol. Catal. B: Enzym.* **2014**, *110*, 87–91; (b) Chen, Y.; Zhuo, J.; Zheng, D.; Tian, S.; Li, Z. *J. Mol. Catal. B: Enzym.* **2014**, *106*, 100–104.
12. Shahane, S.; Louafi, F.; Moreau, J.; Hurvois, J.-P.; Renaud, J.-L.; van de Weghe, P.; Roisnel, T. *Eur. J. Org. Chem.* **2008**, 4622–4631.
13. (a) Carr, R.; Alexeeva, M.; Enright, A.; Eve, T. S. C.; Dawson, M. J.; Turner, N. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4807–4810; (b) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. *J. Am. Chem. Soc.* **2013**, *135*, 10863–10869.