Process Biochemistry xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Process Biochemistry

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

Stereo-complementary bioreduction of saturated *N*-heterocyclic ketones

Chao Li[a,b,c], Yan Liu[a,b], Xiao-Qiong Pei[a,b], Zhong-Liu Wu[a,b,*]

[a] *Key Laboratory of Environmental and Applied Microbiology, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China*
[b] *Environmental Microbiology, Key Laboratory of Sichuan Province, Chengdu 610041, China*
[c] *Graduate University of the Chinese Academy of Sciences, Beijing 100049, China*

ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form 27 February 2017
Accepted 1 March 2017
Available online xxx

Keywords:
Ketoreductase
Hydroxypiperidine
Hydroxypyrrolidine
Hydroxyazepane
Bioreduction

Chemical compounds studied in this article:
tert-butyl 3-oxopyrrolidine-1-carboxylate (PubChem CID: 471360)
(*S*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (PubChem CID: 854055)
(*R*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (PubChem CID: 6544479)
1-benzylpyrrolidin-3-one (PubChem CID: 69890)
(*S*)-1-benzylpyrrolidin-3-ol (PubChem CID: 2733875) ;(*R*)-1-benzylpyrrolidin-3-ol (PubChem CID: 643472)
benzyl 3-oxopyrrolidine-1-carboxylate (PubChem CID: 561203)
(*S*)-benzyl 3-hydroxypyrrolidine-1-carboxylate (PubChem CID: 13438604)
(*R*)-benzyl 3-hydroxypyrrolidine-1-carboxylate (PubChem CID: 11183628)
ethyl 3-oxopyrrolidine-1-carboxylate (PubChem CID: 277754)
(*S*)-ethyl 3-hydroxypyrrolidine-1-carboxylate (PubChem CID: 66772749)
(*R*)-ethyl 3-hydroxypyrrolidine-1-carboxylate (PubChem CID: 66291444)

ABSTRACT

The asymmetric bioreduction of several saturated *N*-heterocyclic ketones is demonstrated in a stereo-complementary fashion using the ketoreductases READH and *Ch*KRED20 for the production of (*S*)- and (*R*)-alcohols, respectively. The reaction accepts substrates with a five-, six- or seven-membered ring,

* Corresponding author at: Chengdu Institute of Biology, Chinese Academy of Sciences, 9 South Renmin Road, 4th Section, Chengdu 610041, Sichuan, China. Tel.: +86 28 82890434.
E-mail address: wuzhl@cib.ac.cn (Z.-L. Wu).

http://dx.doi.org/10.1016/j.procbio.2017.03.002
1359-5113/

tert-butyl 3-oxopiperidine-1-carboxylate (PubChem CID: 2756825)
(*S*)-*tert*-butyl 3-hydroxypiperidine-1-carboxylate (PubChem CID: 1514399)
(*R*)-*tert*-butyl 3-hydroxypiperidine-1-carboxylate (PubChem CID: 1514398)
1-benzylpiperidin-3-one (PubChem CID: 96650)
(*S*)-1-benzylpiperidin-3-ol (PubChem CID: 693762)
(*R*)-1-benzylpiperidin-3-ol (PubChem CID: 693761)
benzyl 3-oxopiperidine-1-carboxylate (PubChem CID: 1514169)
(*S*)-benzyl 3-hydroxypiperidine-1-carboxylatel (PubChem CID: 6932653)
(*R*)-benzyl 3-hydroxypiperidine-1-carboxylate (PubChem CID: 6932652)
tert-butyl 4-oxoazepane-1-carboxylate (PubChem CID: 1512679)
(*S*)-*tert*-butyl 4-hydroxyazepane-1-carboxylate (PubChem CID: 40481276)
(*R*)-*tert*-butyl 4-hydroxyazepane-1-carboxylate (PubChem CID: 40481277)
1-benzylazepan-4-one (PubChem CID: 1514350)
(*S*)-1-benzylazepan-4-ol (PubChem CID: 1514352)
(*R*)-1-benzylazepan-4-ol (PubChem CID: 1514351)
benzyl 4-oxoazepane-1-carboxylate (PubChem CID: 1512681)
(*S*)-benzyl 4-hydroxyazepane-1-carboxylate (PubChem CID: 51892891)
(*R*)-benzyl 4-hydroxyazepane-1-carboxylate (PubChem CID: 51892892)
tert-butyl 3-oxoazepane-1-carboxylate (PubChem CID: 22831870)
(*S*)-*tert*-butyl 3-hydroxyazepane-1-carboxylate (PubChem CID: 73424851)
(*R*)-*tert-butyl* 3-hydroxyazepane-1-carboxylate (PubChem CID: 73424814)
1-benzylazepan-3-one (PubChem CID: 15152264)
1-benzylazepan-3-ol (PubChem CID: 22933843).

and exhibits excellent stereoselectivity when using 2-propanol as both the ultimate reducing agent and cosolvent, achieve >99% ee in the majority of cases for both enantiomers.

1. Introduction

Optically pure saturated *N*-heterocyclic alcohols, such as hydroxypiperidine and hydroxypyrrolidine, are important building blocks for the synthesis of a variety of natural compounds and pharmaceutically relevant products including some marketed drugs [1–3]. They are mainly prepared from chiral pools through time-consuming multi-step chemical conversions, or enzymatic kinetic resolution via hydrolysis or acylation [4–6], or from chiral azido-containing precursors that are synthesized from azido-aldehydes, using aldolases [7]. On the other hand, the corresponding ketone precursors of many saturated *N*-heterocyclic alcohols are commercially available, which would make asymmetric reduction a convenient choice to provide a concise and atom economic approach.

However, despite of the well-documented asymmetric reduction of aromatic ketones, it still lacks efficient catalytic systems to prepare aliphatic alcohols, including *N*-heterocyclic alcohols, with high enantioselectivity. Li et al. have reported a novel chiral surfactant-type catalyst to achieve the asymmetric transfer hydrogenation of aliphatic ketones, resulting in good to excellent conversions and stereoselectivities [8]. However, for the substrate *N*-Boc-3-oxopyrrolidine (**1a**), the enantiopurity of the product (*R*)-*N*-Boc-3-hydroxypyrrolidine (**1b**) was only 92% ee even at strictly controlled reaction temperatures as low as 5 °C [8].

As a potential alternative to chemical strategies, the tissue of *Daucus carota* has been applied to catalyze the Prelog-reduction

Please cite this article in press as: C. Li, et al., Stereo-complementary bioreduction of saturated *N*-heterocyclic ketones, Process Biochem (2017), http://dx.doi.org/10.1016/j.procbio.2017.03.002