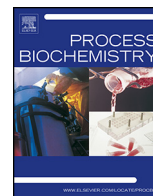




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Stereo-complementary bioreduction of saturated *N*-heterocyclic ketones

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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,

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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-carboxylate
(PubChem CID: 6932653)
(*R*)-benzyl
3-hydroxypiperidine-1-carboxylate
(PubChem CID: 6932652)
tert-butyl 4-oxazepane-1-carboxylate
(PubChem CID: 1512679)
(*S*)-*tert*-butyl
4-hydroxazepane-1-carboxylate
(PubChem CID: 40481276)
(*R*)-*tert*-butyl
4-hydroxazepane-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-oxazepane-1-carboxylate
(PubChem CID: 1512681)
(*S*)-benzyl
4-hydroxazepane-1-carboxylate
(PubChem CID: 51892891)
(*R*)-benzyl
4-hydroxazepane-1-carboxylate
(PubChem CID: 51892892)
tert-butyl 3-oxazepane-1-carboxylate
(PubChem CID: 22831870)
(*S*)-*tert*-butyl
3-hydroxazepane-1-carboxylate
(PubChem CID: 73424851)
(*R*)-*tert*-butyl
3-hydroxazepane-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.

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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

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