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Clean Enzymatic Production of Ursodeoxycholic Acid Enabled by a Newly Identified NADH-dependent 7β-Hydroxysteroid Dehydrogenase

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PURPOSE OF THE ABSTRACT
7β-Hydroxysteroid dehydrogenases (7β-HSDHs) play an important role in the enzymatic synthesis of ursodeoxycholic acid (UDCA), which is a value-added compound with a range of pharmacological activities. Since the cofactor NADH is much cheaper than NADPH, the production of UDCA using an NADH-dependent 7β-HSDH has better prospects than that using an NADPH-dependent 7β-HSDH. However, a major bottleneck in UDCA biosynthesis is the poor catalytic activity of the current NADH-dependent 7β-HSDHs. In this work, a new and natively NADH-dependent Rs7β-HSDH from Roseococcus sp. was identified, which showed a high specific activity of 63.3 U mg−1protein toward 7-oxo-lithocholic acid, with a catalytic efficiency (kcat/KM) of 515 mM–1 s–1. In a preparative biotransformation (100-mL scale) using Rs7β-HSDH and an NAD+-dependent 7α-HSDH, with O2/NOX and HCOO−/FDH systems for the regeneration of cofactors (NAD+ and NADH), 25 mM chenodeoxycholic acid was completely converted to UDCA in one-pot two-step cascade, with an 80% isolated yield and a total turnover number (TTN) of 6586 for Rs7β-HSDH. The environmental factor (E-factor) of this process was 8.37 when water was excluded, much lower than those obtained from other processes reported so far, indicating a great potential of this Rs7β-HSDH for more sustainable and cleaner enzymatic production of UDCA.

FIGURES

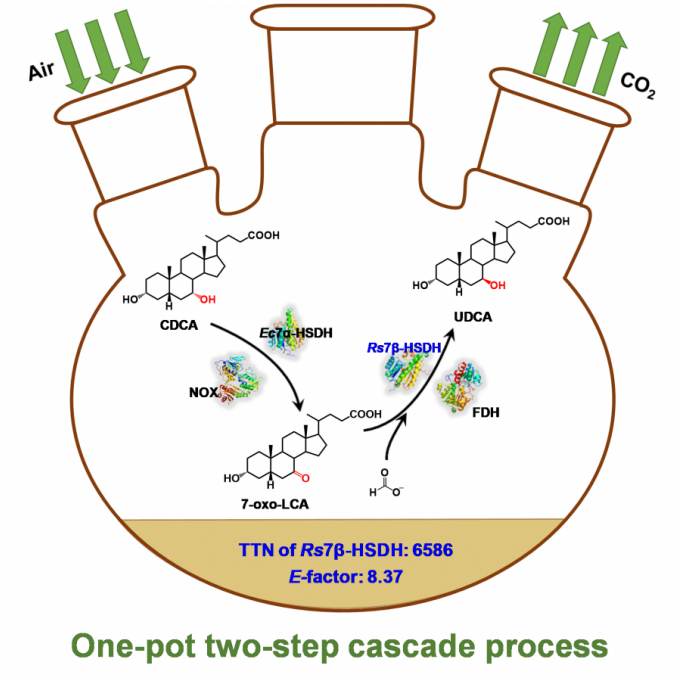

FIGURE 1

Abstract graphic

One-pot synthesis of ursodeoxycholic acid using dual NAD-dependent HSDHs, NOX and FDH for cofactor regeneration makes this cascade process green and clean.

FIGURE 2

KEYWORDS

Ursodeoxycholic acid | 7β-Hydroxysteroid dehydrogenase | NADH dependency | Cofactor regeneration

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