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Chemoenzymatic synthesis of *d*-biotin intermediate lactone via lipase-catalyzed desymmetrization of meso diols

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ABSTRACT

A chemoenzymatic methodology for the asymmetric synthesis of *d*-biotin intermediate lactone ((3a*S*, 6a*R*)-tetrahydro-1,3-dibenzylhexahydro-1*H*-Furo[3,4-d] imidazole-2,4-dione) **1** has been demonstrated. The key step of the synthetic routes is Lipozyme RM IM catalyzed desymmetrization of meso-diols **3**. The highest enantiomeric excess (*e.e.* > 98%) and yield (>90%) of the product was achieved with Lipozyme RM IM in Dioxane/Toluene (1:3, v/v) at 35 °C. Furthermore, Lipozyme RM IM showed an excellent operational stability, retaining above 80% of the initial activity after 10 cycles of reaction. *d*-Biotin intermediate lactone **1** was obtained subsequently by Jones oxidation, basic hydrolysis and lactonization.

1. Introduction

d-Biotin (Vitamin H) is a water-soluble vitamin B which is essential to the normal physiological activities of animals and human life. It serves as the prosthetic group of some metabolic enzymes in vivo known as biotin-dependent carboxylases [1–3]. Growth retardation and dysontogenesis will occur when poultry lack biotin. *d*-Biotin has been extensively applied in medicine and health protection, particularly as the feedstuff additive with large commercial requirement. *d*-Biotin intermediate (3a*S*, 6a*R*)-lactone **1** is extremely vital to the synthesis of *d*-biotin [4,5]. Many scientists devoted themselves to the synthesis of (3a*S*, 6a*R*)-lactone **1**, and the asymmetric synthetic routes of (3a*S*, 6a*R*)-lactone **1** have been numerously reported in recent years. Fei Xiong et al. obtained the (3a*S*, 6a*R*)-lactone **1** through a rapid cinchona alkaloid-based sulfonamide-mediated enantioselective alcoholysis of meso-cyclic anhydride [6]. A method through catalytic reactivity in the hydrogenation of a cyclic anhydride to a biotin synthetic intermediate has been investigated using Wilkinson Ru complex by Masahiro Yoshimura et al. [7].

With the development of enzymatic reactions in organic chemistry, more and more chemists pay attention to the study of enzymatic desymmetrization. Due to the ecological aspect of reaction, enzymatic reactions have an advantage status of green chemistry over chemical synthesis [8]. Because of being carried out under mild conditions, enzymatic reactions have the advantage of less side reaction (such as isomerization, racemization, epimerization, and rearrangement of molecules). Enzymatic synthesis of (3a*S*, 6a*R*)-lactone **1** via asymmetric hydrolysis of meso-dicarboxylic esters by pig liver esterase and subsequently following by Grignard reaction was reported [9,10]. Zheng et al. reported that (3a*S*, 6a*R*)-lactone **1** could be efficiently prepared in excellent conversion ratio ($c \geq 40\%$) and enantiomeric purities (*e.e.* $\geq 98\%$) via enantioselective lactonization by the resting cell of *Aspergillus oryzae* WZ007 [11].

Hydrolases have been successfully used for the desymmetrization of different meso or prochiral alcohols, carboxylic acid esters, anhydrides and nitriles [12]. Many authors have demonstrated that enzymatic desymmetrization of the prochiral dimethyl carbonate is a versatile and effective way to obtain the corresponding monoester [13,14]. Two approaches have been employed for the desymmetrization of different meso or prochiral alcohols: acylation of the free alcohol by means of transesterification reaction [15,16], and hydrolysis of an appropriate acyl derivative of alcohol [17,18]. Lipase-catalyzed transesterification may be an efficient method for desymmetrization of meso-diols [19–22].

In this paper, we described a novel synthetic route of (3a*S*, 6a*R*)-lactone **1** by enantioselective transesterification of diols **3** with Lipozyme RM IM and subsequently following Jones oxidation, basic hydrolysis and lactonization (Scheme 1).

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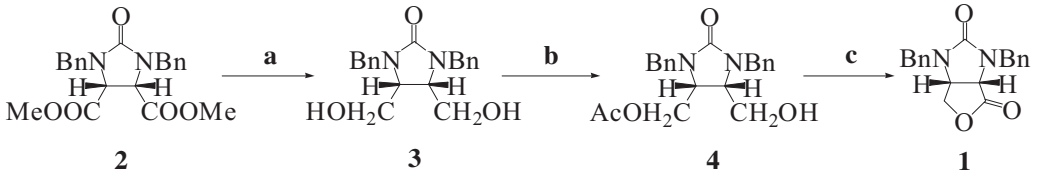

Scheme 1. Synthetic scheme for the synthesis of *d*-biotin intermediate lactone **1**. Reaction conditions: (a) EtOH, $NaBH_4$, 0 °C to r.t. 50 °C, reflux 3 h 96%; (b) Lipozyme RM IM, Dioxane/Toluene (1:3), 6 h, 35 °C, 90%; (c) CrO_3, H_2SO_4, H_2O, acetone, 0 °C, 2 h, then 2 M NaOH, 1 M HCl reflux, 3 h, 65%.

2. Experimental

2.1. General methods

The conversions were determined by Waters 1525 HPLC with a UV detector. Enantiomeric separation of monoacetate **4** was performed using the Chiralcel AD-H column (250 mm × 4.6 mm, 10 μm, Daicel, Japan) and a mixture of hexane and propan-2-ol 80:20 (v/v) as eluant. Flow rate was 0.8 mL/min and retention times for (4*R*, 5*S*)-monoacetate-**4** and (4*S*, 5*R*)-monoacetate-**4** were 19.5 and 23.1 min, respectively. Enantiomeric separation of lactone **1** was performed using the Chiral CD-Ph column (250 mm × 4.6 mm, 10 μm, Shiseido, Japan) and a mixture of acetonitrile and water 60:40 (v/v) as eluant. Flow rate was 0.5 mL/min and retention times for (3a*R*, 6a*S*)-lactone-**1** and (3a*S*, 6a*R*)-lactone-**1** were 12.8 and 14.2 min, respectively. ^{1}H NMR spectra were recorded on a Bruker 500 Hz apparatus (TMS as an internal standard, ^{13}C NMR 125 Hz). Mass spectra were recorded on an Esquire 6000 spectrometer. IR spectra were recorded on Bruker Tensor 27 spectrometer. Optical rotations were determined using an Autopol IV Polarimeter at 25 °C using a cell of 1 dm length.

2.2. Materials

Meso diester **2** and *d*-biotin intermediate lactone **1** was obtained from Zhejiang Shengda Pharmaceutical Co., Ltd. (Zhejiang, China) as a gift. Commercially available organic solvents were treated with 3 Å molecular sieves. All other chemicals employed in this work were obtained from various commercial suppliers.

Novozym 435 (component B of the lipase from *Candida Antarctica* immobilized on macroporous polyacrylate resin), Lipozyme RM IM (*Rhizomucor miehei* immobilized on ionic resin) were supplied by Novozymes A/S (Bagsvaerd, Denmark). Amano lipase AK (*Pseudomonas fluorescens* lipase), Amano lipase A (*Aspergillus niger* lipase), *Rhizopus niveus* lipase, Amano PS IM (lipase from *Burkholderia cepacia* immobilized on diatomaceous earth), and Amano lipase AY (*Candida rugosa* lipase) were obtained from Sigma–Aldrich (shanghai) Trading Co. Ltd. (shanghai, China). Lipase from pig (porcine) pancreas (PPL) was obtained from Aladdin Industrial Co. (shanghai, China).

Jones reagent was prepared as follows: chromium trioxide (26.7 g) was dissolved in sulfuric acid (23 mL) and the resulting mixture was diluted with water to 100 mL.

2.3. Procedure for the synthesis of **3** [23]

A solution of diester **2** (9.53 g, 24.9 mmol) in anhydrous CH_3COOH (200 mL) was cooled to 0 °C and $NaBH_4$ (11.3 g, 30.5 mmol) was carefully added during 10 min. The reaction mixture was stirred for 5 h at room temperature, followed by refluxing for 3 h at 80 °C. And then formic acid was dripped to the above solution slowly until pH fell to about 4–5 at 0 °C. Salts were filtered off through buchner funnel, and the residue was washed with CH_3COOH (3 mL × 20 mL), filtrate was combined and evaporated under reduced pressure, the obtained reaction crude that was purified by recrystallization from *n*-hexane affording 7.63 g of meso-diols **3** as a white solid (94%): ^{1}H NMR($CDCl_3$): δ 7.36–7.27 (m, 10H), 4.92–4.89 (d, 2H, J = 15.40 Hz), 4.14–4.11 (d, 2H, J = 15.45 Hz), 3.84–3.82 (d, 2H, J = 13.00 Hz), 3.75–3.72 (d, 2H, J = 12.90 Hz), 3.51 (s, 2H), 2.37 (s, 2H); ^{13}C NMR($CDCl_3$): δ 161.5, 137.1, 128.8, 127.9, 127.8, 127.6, 57.7, 56.5, 46.6, 45.6; MS (*m*/*z*) 349 $(M + Na)^+$; IR ν_{max} (cm^{-1}): 3442, 3266, 2930, 1670, 1476, 1453, 1359, 1253, 1146, 1054, 1001, 741, 701, 657, 540.

2.4. Procedure for the synthesis of **4**

2.4.1. General procedure for the chemical synthesis of racemic monoacetates **4**

To a solution of diols **3** (2.76 mmol) in dry CH_2Cl_2 (28 mL) were added Et_3N (120 μL, 8.40 mmol) and DMAP (111 mg, 0.90 mmol) under nitrogen atmosphere. After the mixture was stirred for a couple of minutes, Ac_2O (265 μL, 2.8 mmol) was added in portions, and the solution was stirred for an additional 4 h at room temperature. After the solvent was evaporated under reduced pressure, the obtained reaction crude that was purified by flash chromatography (EtOAc/petroleum benzene = 2:1) affording the monoacetate **4** as a colorless oil (54% yield): Rf (EtOAc/petroleum benzene = 2:1) 0.46.

2.4.2. General procedure for the lipase-catalyzed synthesis of monoacetates **4**

A mixture of meso-diols **3** (326 mg, 1 mmol), Lipozyme RM IM (100 mg), and vinyl acetate (555.4 μL, 6 mmol) was stirred in 10 mL Dioxane and Toluene (1:3) at 35 °C for 6 h in water baths shaker. After removal of polymer-supported enzyme by filtration, the filtrate was evaporated under reduced pressure. Then the monoacetate **4** was obtained in a yield of 90% with the high enantiomeric excess (*e.e.* > 98%). $[\alpha]^{25}_D$:−7.2(c 1.0 $CHCl_3$); ^{1}H NMR($CDCl_3$): δ 7.34–7.31 (m, 6H), 7.29–7.26 (m, 4H), 4.87 (d, 2H, J = 15.45 Hz), 4.77 (d, 2H, J = 15.40 Hz), 4.44 (d, 2H), 4.42 (d, 2H), 3.45 (s, 2H), 1.98 (s, 1H), 1.98(s, 3H); ^{13}C NMR($CDCl_3$): δ 170.3, 161.2, 137.4, 137.1, 128.7, 128.6, 128.0, 127.9, 127.8, 127.5, 127.4, 61.6, 58.8, 56.4, 54.1, 54.0, 46.3, 46.2, 21.0, 20.7, 14.1. MS (*m*/*z*) 391 $(M + Na)^+$; IR ν_{max} (cm^{-1}): 3354, 2901, 1744, 1658, 1477, 1451, 1356, 1231, 1044, 760, 739, 700, 457 (Scheme 2).

2.5. Procedure for the synthesis of **5**

To a solution of the corresponding diols **3** (2.76 mmol) in dry CH_2Cl_2 (28 mL) were successively added Et_3N (2.34 mL, 16.62 mmol), DMAP (222 mg, 1.84 mmol), and Ac_2O (1.04 mL, 11.08 mmol) under nitrogen atmosphere. The reaction was stirred at room temperature during 4 h until complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was finally purified by flash chromatography on silica gel (EtOAc/petroleum benzene = 2:1), yielding the corresponding diacetate **5** as an oil (98%): Rf (EtOAc/petroleum benzene = 2:1) 0.69; ^{1}H NMR($CDCl_3$): δ 7.36–7.28 (m, 10H), 4.87 (d, 2H, J = 15.45 Hz), 4.33–4.32 (m, 2H, J = 5.15 Hz), 4.30–4.29 (m, 2H, J = 5.05 Hz), 4.23 (s, 1H) 4.19 (s, 1H), 3.67 (s, 2H), 2.02 (s, 6H); ^{13}C NMR($CDCl_3$): δ 170.2, 160.6, 137.1,