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# A novel synthetic strategy for the stereospecific total synthesis of (±)-biotin

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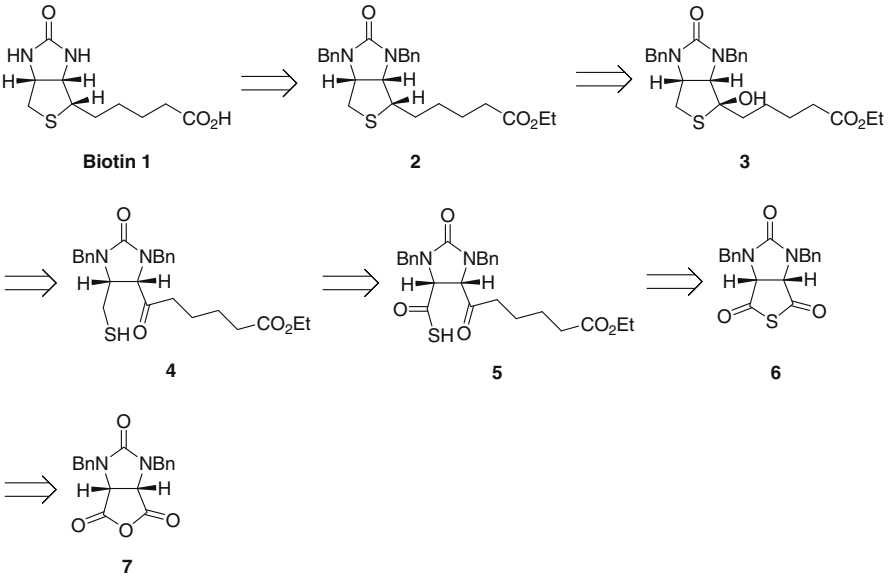
ABSTRACT

A concise and efficient TEA-mediated desymmetrization of *meso*-thioanhydride **6** with 5-ethoxy-5-oxopentylzinc bromine has been developed, which affords a convenient strategy for the stereospecific total synthesis of (±)-biotin **1**.



Due to its unique molecular structure and significant biological properties for human nutrition and animal health, the total chemical synthesis of biotin **1**, a member of important water-soluble B-complex group of vitamins, has become indispensable to both industry and academia.[1] Since the first successful example was reported by Goldberg and Sternbach at F. Hoffmann-La Roche company in 1949, tremendous advances in the development of various synthetic approaches toward this vitamin have been achieved.[2] As part of our ongoing research in this field,[3] herein we describe a facile and convenient total synthesis of **1** which involves a novel strategy via a desymmetrization of *meso*-thioanhydride with carbon-based nucleophile.

In our retrosynthetic analysis, we reasoned that the selective ionic hydrogenation of *meso*-thiolactol **3** would provide **2**, the direct precursor to biotin **1** (Scheme 1). *meso*-Thiolactol **3** would then in turn be accessed from **4** via a acid-catalyzed intramolecular cyclization. Intermediate **4** could be available from the chemoselective reduction of the carboxyl group in compound **5** which in




**Scheme 1.** Retrosynthetic analysis of (±)-biotin.

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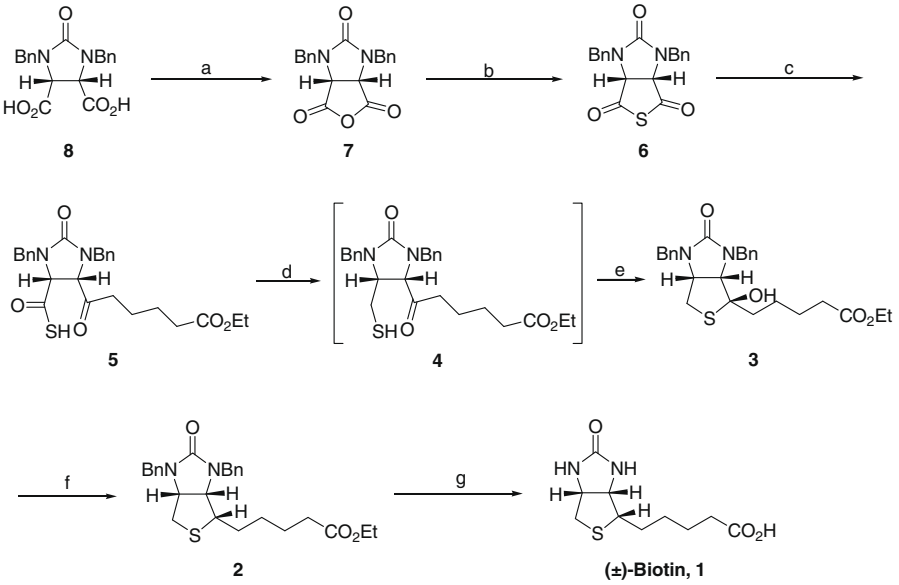


**Scheme 2.** Reagents and conditions: (a) $SOCl_2$, reflux, 4 h, 98%; (b) $Na_2S{\cdot}9H_2O$, THF, $H_2O$, rt, 49%; (c) $Br(CH_2)_4CO_2Et$, Zn, DMF, THF, toluene, TEA, 25 °C; (d) cyanuric chloride, NMM, THF, $NaBH_4$, 25 °C to 0 °C; (e) 2 N aq HCl, 25 °C, 82% (from **6** to **3**); (f) $Et_3SiH$, TFA, DCM, 25 °C, 91%; (g) 47% HBr, xylene, reflux, then triphosgene, activated charcoal, 80%.

turn would be produced in a straightforward one-pot sequence from desymmetrization of the *meso*-thioanhydride **6** with C-5 functionalized carbon-based nucleophile (5-ethoxy-5-oxopentylzinc bromine). Compound **6** could be directly elaborated from *meso*-cyclic anhydride **7** following a protocol reported previously.[3c,4]

Our synthesis commenced with the preparation of *meso*-cyclic anhydride **7** from the commercially available *cis*-1,3-dibenzyl-2-imidazolidone-4, 5-dicarboxylic acid (**8**) as outlined in Scheme 2. Treatment of *meso*-dicarboxylic acid **8** with $SOCl_2$ at refluxing temperature under solvent-free conditions afforded the *meso*-cyclic anhydride **7** in nearly quantitative yield,[5] which was quantitatively converted into *meso*-thioanhydride **6** with a 99% purity upon treatment with $Na_2S{\cdot}9H_2O$ in THF at room temperature.

With the *meso*-thioanhydride **6** in hand, our attention was turned to explore an efficient and straightforward process for the installation of the pentanoic acid side chain on biotin skeleton through a desymmetrization of **6** with carbon-based nucleophile. Thus, the TEA-mediated ring opening of **6** with organozinc reagent, in situ prepared from ethyl 5-bromopentanoate and zinc powder, was conducted in a mixed solvents of DMF/THF/toluene at 35 °C. As expected, this reaction proceeded smoothly to afford the ring-opening product **5**.[6] The carbonyl group of **5** was then chemoselectively reduced with $NaBH_4$ in THF at 0 °C after derivation of the thiohydroxy group with cyanuric chloride in the presence of *N*-methylmorpholine to afford thiol **4**, subsequent treatment with 2 N aq HCl via acid-catalyzed intramolecular cyclization afforded the key intermediate *meso*-thiolactol **3** in 82% overall yield[7] and its $^1H$ NMR and mass spectra were in agreement with those we previously reported.[3l] The ionic hydrogenation of **3** was realized at room temperature by reacting with $Et_3SiH$ in the presence of the TFA to afford the desired pentanoate **2** in 91% yield.[3k] Finally, (±)-biotin **1** was achieved by subjecting **2** to simultaneous debenzylation and ester hydrolysis with 47% aq HBr followed by in situ treatment of the resulting diamine·2HBr with triphosgene in 80% yield after recrystallization from $H_2O$.[3k] The NMR ($^1H$ and $^{13}C$) and mass spectra data for **1** matched well with those of authentic (+)-biotin.

In summary, we have uncovered a novel desymmetrization strategy for the stereospecific total synthesis of (±)-biotin **1**. This method should be of great value in terms of simplicity in elaboration of the pentanoic acid side chain of biotin skeleton. Investigation of the structurally diverse set of chiral ligands to fulfill the enantioselective desymmetrization of *meso*-thioanhydride **6** in optically pure form to accomplish the asymmetric total synthesis of (+)-biotin is currently under way and the results will be reported in due course.

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5. *Synthesis of* **7**: A mixture of **8** (3.54 g, 10 mmol) and thionyl dichloride (7.3 mL, 100 mmol) was stirred under reflux for 4 h. The mixture was cooled down to 25 °C and the precipitated crystals formed were filtered and dried at 80 °C in vacuo for 3 h to give colorless product **7** (3.3 g, 98%) as a white powder. Mp 237.1–237.8 °C (Lit.:[3c] 236–238 °C).
6. *Synthesis of* **5**: To a suspension of zinc powder (1.62 g, 24.8 mmol) in anhydrous DMF (8 mL) was added iodine (0.2 g, 0.8 mmol) under nitrogen atmosphere and the mixture was heated to 80 °C. Ethyl 5-bromopentanoate (3.45 g, 16.5 mmol)

was then added dropwise and the resulting mixture was kept stirring at 80 °C for 4 h. After cooling the mixture to 25 °C, a solution of **6** (2.11 g, 6 mmol) in THF (10 mL) and toluene (10 mL) was added dropwise to a mixture of the 5-ethoxy-5-oxopentylzinc bromine in $Et_3N$ (0.8 mL, 6 mmol). The reaction mixture was stirred for 24 h at 35 °C, and then the reaction was quenched with saturated aq $NH_4Cl$ (25 mL). 2 N aq NaOH (30 mL) was added to the mixture, and the aqueous layer was washed with $Et_2O$. The aqueous layer was acidified with 2 N aq HCl and extracted with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product **5**, which was subjected to next step without further purification.

7. *Synthesis of* **3**: To a solution of cyanuric chloride (1.66 g, 9 mmol) in THF (25 mL) at 25 °C was added *N*-methylmorpholine (0.79 g, 7.8 mmol), and then the solution of **5** (2.89 g, 5 mmol) in THF (25 mL) was added in one portion into the mixture. After stirring for 3 h, the reaction mixture was filtered and a solution of $NaBH_4$ (0.48 g, 12.6 mmol) in $H_2O$ (11 mL) was added dropwise into the filtrate at 0 °C. The resulting mixture was stirred for 10 min after which 2 N aq HCl (55 mL) was added to the mixture. The resulting mixture was stirred at 25 °C for 3 h and then extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (AcOEt/PE = 2/1) to afford **3** (2.30 g, 82%) as a colorless oil. IR (KBr): $\nu$ = 2961, 2594, 1670, 1387, 1259, 665 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ = 7.24–7.32 (m, 10H), 5.10 (d, 1H, $J$ = 15.6 Hz), 4.88 (d, 1H, $J$ = 15.6 Hz), 4.10–4.20 (m, 4H), 4.02 (d, 1H, $J$ = 22.4 Hz), 3.94 (d, 1H, $J$ = 22.4 Hz), 3.65 (m, 1H), 2.72 (m, 2H), 2.24–2.33 (m, 4H), 1.60–1.62 (m, 2H), 1.44–1.45 (m, 2H), 1.23–1.27 (m, 3H); ESI-MS $m/z$ 469 $[M+H]^+$.