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Facile synthesis of (+)-biotin via Fukuyama coupling reaction

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Abstract

Treatment of a thiolactone **2** with a zinc reagent **3** in the presence of $PdCl_2(PPh_3)_2$ (10 mol%) allowed installation of a C-2 side chain of (+)-biotin in a highly efficient manner, which enabled synthesis of (+)-biotin in three steps from **2**. © 2000 Elsevier Science Ltd. All rights reserved.

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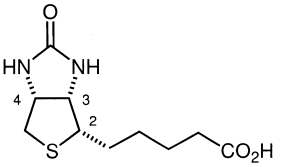
(+)-Biotin **1** has received considerable attention as an important vitamin for human nutrition and animal health.[1] Since the first total synthesis of (+)-biotin was accomplished about 50 years ago, a number of synthetic methods have been developed.[2] Among them, a method utilizing thiolactone **2** as a key intermediate has been one of the most reliable approaches so far developed.[3] The method is, however, not entirely satisfactory because a number of steps (six steps from **2** to (+)-biotin) are needed for introducing the C-2 side chain to the thiolactone **2**. Some improvements for the installation of the C-2 side chain to the thiolactone **2** have been reported which involve: (1) treatment with butylenedimagnesium chloride followed by in situ reaction with carbon dioxide;[4] (2) reaction with 4-(2,4,10-trioxaadamantyl)butylmagnesium bromide;[5] and (3) Wittig reaction using 4-carboxybutyltriphenylphosphonium bromide.[6] Although these methods can provide (+)-biotin in two to three steps less than the original one, they need a much lower reaction temperature (ca. –30°C) and/or expensive reagents.



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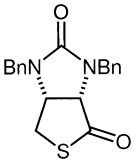

2

Fukuyama and co-workers have recently developed a novel ketone synthesis by a palladium-catalyzed reaction of thiol esters with zinc reagents.[7] We envisioned a possible use of the Fukuyama

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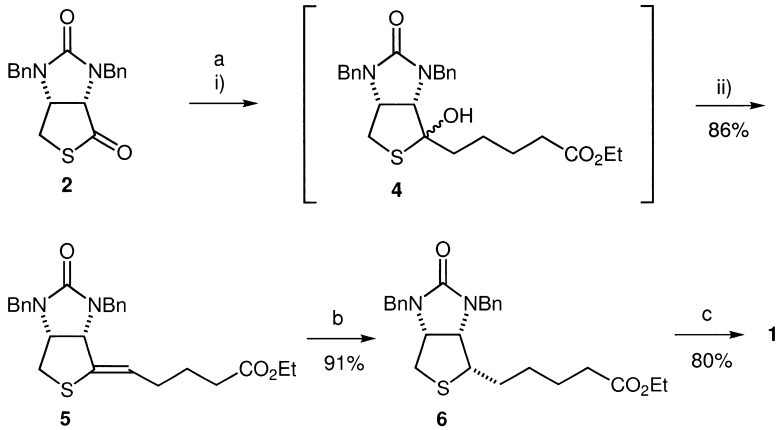
coupling reaction for the installation of the C-2 side chain. Reported herein is a successful result which realized the efficient synthesis of (+)-biotin from the thiolactone **2** via the Fukuyama coupling reaction.

The zinc reagent **3**[8] corresponding to the C-2 side chain was prepared from an iodide which can be derived in a single step from δ-valerolactone.[9,10] Treatment of the thiolactone **2** with the zinc reagent **3** (3 equiv.) in the presence of $PdCl_2(PPh_3)_2$ (10 mol%) in a mixed solvent of THF, toluene and DMF at 20°C for 35 h gave an alcohol **4** which, without purification, was allowed to react with *p*-TsOH·H_2O (0.4 equiv.) in toluene at 20°C for 18 h to afford 4-ethoxycarbonylbutylidene derivative **5** in 86% yield, exclusively, as a *Z*-isomer (Scheme 1).[11,13] The compound **5** was converted to (+)-biotin **1** according to the reported procedure[3] through hydrogenation and subsequent removal of the benzyl protective groups (73%, two steps). The product **1** obtained by the present method revealed identity with an authentic sample with respect to mp, IR, ^{1}H NMR, mass spectra and specific rotation (mp 230–231°C, $[\alpha]_D^{25}$ +90.2 (*c* 1.01, 0.1 N NaOH) (lit.[14] mp 229.5–230°C, $[\alpha]_D^{25}$ +91.3 (*c* 1.00, 0.1 N NaOH).



Scheme 1. a: (i) $IZn(CH_2)_4CO_2Et$ (3 equiv.) (**3**), $PdCl_2(PPh_3)_2$ (10 mol%), THF, toluene, DMF, 20°C, 35 h; (ii) p-TsOH, toluene, 20°C, 18 h; b: H_2 (70 atm)/Pd-C, EtOH, 100°C, 3 h; c: (i) 48% aq. HBr, reflux, 48 h; (ii) $ClCO_2ET$, NaOH; (iii) HCl.

In conclusion, a facile and efficient synthesis of (+)-biotin from the thiolactone **2** via the Fukuyama coupling reaction was accomplished. The present method can provide (+)-biotin in 63% overall yield in three steps from the thiolactone **2**, which is three steps shorter than the conventional method based on the Grignard reaction.[3] The short steps, high yield, simple operations, ready availability of the reagents and mild reaction conditions would provide a practical access to (+)-biotin. Further improvements of the present synthesis are under current investigation and will be reported elsewhere in due course.

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9. Ethyl 5-iodopentanoate was prepared from δ-valerolactone with some modification of the reported methods:[10] Into a solution of δ-valerolactone (200 g, 2 mol) in CH_3CN (1000 mL) was added NaI (330 g, 2.2 mol) followed by TMS–Cl (239 g, 2.2 mol) at 25–30°C and the mixture was stirred at the same temperature for 24 h. Ethanol (400 mL) was added and the mixture was stirred at 25–30°C for 6 h. The mixture was evaporated in vacuo and the residue was partitioned with AcOEt and water. The organic phase was separated and washed with 10% aq. $Na_2S_2O_3$ and water, dried over $MgSO_4$ and evaporated. The residue was purified by distillation (bp 85–87°C/3 mmHg) to give the iodide (434 g, 85%).
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11. Experimental procedure: Into a suspension of zinc powder (activated according to Ref. 12) (1.17 g, 17. 9 mmol) in THF (2.7 mL) was added 1, 2-dibromoethane (40 μL, 0.46 mmol) and the mixture was heated to reflux for 3 min. After cooling the mixture to 25°C, TMS–Cl (40 μL, 0.32 mmol) was added, and the slurry was stirred for 15 min. Ethyl 5-iodopentanoate (1.5 mL, 8.96 mmol) was then added and the mixture was heated to 35°C and stirred for 30 min to afford the zinc reagent **3**. Into the zinc reagent **3** were added thiolactone **2** (1.01 g, 2.98 mmol), toluene (3.5 mL), DMF (0.27 mL) and $PdCl_2(PPh_3)_2$ (209 mg, 0.3 mmol), and the mixture was stirred at 20°C for 35 h. The mixture was filtered through Celite and the filtrate was evaporated. Into the residue was added ether and the mixture was washed successively with 1N HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. The residue was treated with *p*-$TsOH{\cdot}H_2O$ (226 mg, 1.19 mmol) in toluene (31 mL) at 20°C for 18 h. The mixture was diluted with AcOEt and washed successively with sat. aq. $NaHCO_3$, water and brine, dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (hexane:AcOEt = 5:2) to afford **5** (1.16 g, 86%) ($[\alpha]_D^{25}$ +190.9 (*c*, 0.95, MeOH)).
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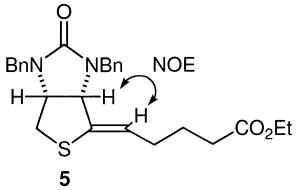
13. The double bond stereochemistry (*Z*-configuration) of **5** was assigned by NOE experiments with ^1H NMR spectroscopy: enhancement (10%) of the signal of the C-3 hydrogen atom was observed in the compound **5** when the olefinic hydrogen was irradiated.



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