

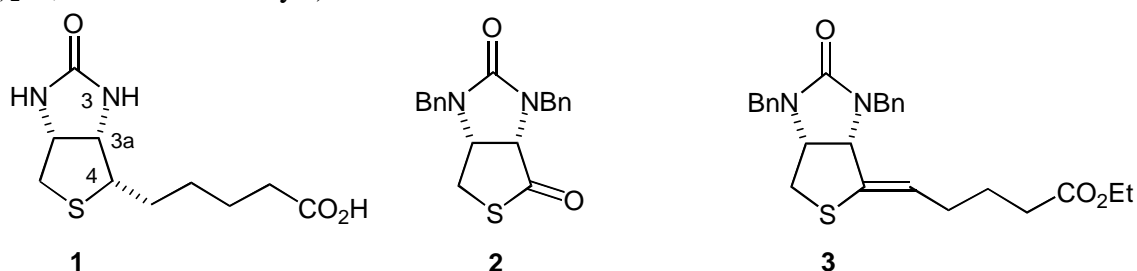
A PRACTICAL SYNTHESIS OF (+)-BIOTIN THROUGH PALLADIUM HYDROXIDE ON CHARCOAL-CATALYZED FUKUYAMA COUPLING REACTION

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Abstract – The Fukuyama coupling reaction of thiolactone (**2**) with 5-ethoxy-5-oxopentylzinc iodide (**4**) in the presence of 0.65 mol% of non pyrophoric palladium hydroxide on charcoal (Pearlman's catalyst) provided a vinyl sulfide (**3**) carrying a C-4 side chain of (+)-biotin (**1**) in 87% yield.

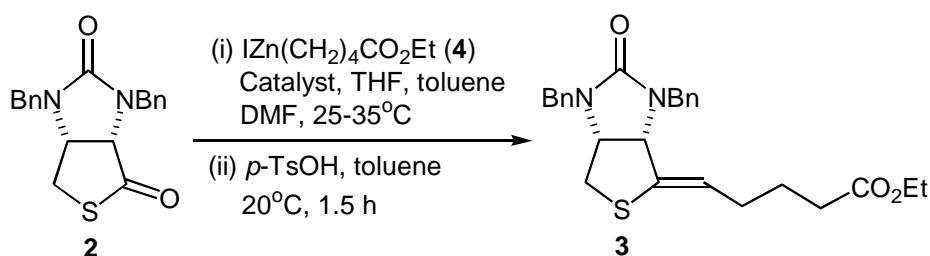
(+)-Biotin (**1**) has received considerable attention because of the useful biological properties for human nutrition and animal health.¹ Among a number of synthetic approaches to **1**,² a method utilizing thiolactone (**2**) as a key intermediate is considered to be most attractive.³ We have recently reported a short step synthesis of **1** *via* Fukuyama coupling reaction⁴ of **2** with 5-ethoxy-5-oxopentylzinc iodide (**4**).⁵ The method, however, requires 5 mol% of pyrophoric palladium on charcoal (Pd/C). From a practical point of view, reducing the amount of the expensive palladium catalyst and eliminating the dangerous operation of adding pyrophoric Pd/C to an organic solvent with a low flash point are highly desirable. Reported herein is an improved method for the installation of the C-4 side chain of **1** through the Fukuyama coupling reaction of **2** with **4** in the presence of non pyrophoric palladium hydroxide on charcoal (Pd(OH)₂/C, Pearlman's catalyst).



¹Dedicated to Professor Albert I. Meyers in celebration of his 70th birthday.

The zinc reagent (**4**) was prepared according to a reported procedure^{5a} and allowed to react with **2** in the presence of the palladium catalyst of varying amount (Table 1). Use of 5 mol% of Pd/C provided the coupling product (**3**) in 92% yield after dehydration with *p*-toluenesulfonic acid (Entry 1). However, reducing the amount of Pd/C to 2 mol% considerably prolonged the reaction period (1.5 to 17 h) to give **3** in 79% yield (Entry 2). While Pd(OH)₂/C has been used as a highly active catalyst for hydrogenolysis of benzylamines⁶ and allylic acetates,⁷ and hydrostannation of alkenes with tributyltin hydride,⁸ its application to carbon-carbon bond forming reactions has never been reported. The catalyst is non pyrophoric prior to exposure to a reducing agent and “Pd/C” that results *in situ* from reduction of Pd(OH)₂/C may be highly active. We thus tested Pd(OH)₂/C for the coupling reaction of **2** with **4**. As expected, the reaction was remarkably accelerated by the use of Pd(OH)₂/C (2.6 mol%) to complete the reaction in 1 h providing **3** in 90% yield (Entry 3). The high reaction rate and yield were as well observed with such a low catalyst loading as 0.65 mol% (87% yield, Entry 5).⁹ To the best of our knowledge, this represents the first example of the use of Pd(OH)₂/C for the carbon-carbon bond forming reactions. The compound (**3**) was converted to (+)-biotin (**1**) in 73% yield according to a reported procedure^{5a} *via* hydrogenation followed by removal of the protective groups.

Table 1. The Fukuyama Coupling Reaction of **2** with **4**.^a



Entry	Catalyst ^b	mol%	Period (h)	Yield (%) ^c
1	Pd/C	5	1.5	92
2	Pd/C	2	17	79
3	Pd(OH) ₂ /C	2.6	1	90
4	Pd(OH) ₂ /C	1.3	2	84
5	Pd(OH) ₂ /C	0.65	2	87
6	Pd(OH) ₂ /C	0.32	3	78

^aThe reactions were conducted on 31 mmol scale. ^bPurchased from Kawaken Fine Chemicals Co., Ltd. ^cIsolated yield.

In conclusion, a highly efficient synthesis of (+)-biotin (**1**) through Pd(OH)₂/C-catalyzed Fukuyama coupling reaction of **2** with **4** was accomplished. The high yield, simple operation and low catalyst

loading would permit a practical access to (+)-biotin of growing significance. Further application of Pd(OH)₂/C to other cross coupling reactions are currently under investigation and will be reported elsewhere in due course.

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9. **Experimental procedure (Table 1, Entry 5):** Into a suspension of zinc powder (Merck, < 45 μm) (7.32 g, 110 mmol) in THF (23 mL) was added 1, 2-dibromoethane (250 μL, 2.9 mmol) and the mixture was refluxed for 5 min. After cooling the mixture to 20°C, TMSCl (250 μL, 2 mmol) was added and the slurry was stirred for 15 min. Ethyl 5-iodopentanoate (24.8 g, 97 mmol) was then added dropwise to the mixture at 30-60°C for 1 h to give a zinc reagent (**4**). Into the mixture containing **4** were added thiolactone (**2**) (10.5 g, 31 mmol), toluene (35 mL), DMF (2.3 mL) and 10% Pd(OH)₂/C (Kawaken Fine Chemicals Co., Ltd.) (218 mg, 0.2 mmol) at 20°C and the mixture was stirred at 25-35°C for 2 h. The mixture was filtered through Celite and the filtrate was washed successively with 1N HCl, sat. aq. NaHCO₃ and brine, dried over anhydrous MgSO₄ and evaporated. The residue dissolved in toluene (78 mL) was treated with *p*-toluenesulfonic acid monohydrate (590 mg, 3.1 mmol) and the mixture was stirred at 20°C for 1.5 h. The mixture was washed with water and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5:2) to give **3** (12.2 g, 87%).