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Synthetic Studies on (+)-Biotin, Part 11:[1] Application of *Cinchona* Alkaloid-Mediated Asymmetric Alcoholysis of *meso*-Cyclic Anhydride in the Total Synthesis of (+)-Biotin

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Abstract: A practical and asymmetric process for the total synthesis of (+)-biotin (**1**) has been accomplished starting from *cis*-1,3-dibenzyl-2-oxoimidazolidine-4,5-dicarboxylic acid (**2**). This approach features a highly enantioselective alcoholysis of *meso*-cyclic anhydride **3** into (4*S*,5*R*)-cinnamyl hemiester **4** mediated by *Cinchona* alkaloids. Another attractive feature of this synthesis involves the use of recyclable palladium nanoparticles-catalyzed assembly of the 4-carboxybutyl chain at C-4 in (3*aS*,6*aR*)-thiolactone **7** employing an improved Fukuyama-type cross-coupling reaction

Keywords: anion exchange resin D296; asymmetric alcoholysis; (+)-biotin; *Cinchona* alkaloids; Fukuyama-type cross-coupling; palladium nanoparticles

Introduction

In the first industrial total synthesis of (+)-biotin (**1**), utilizing (3a*S*,6a*R*)-thiolactone **7** as key building block, developed by Goldberg and Sternbach at Hoffmann-La Roche in 1949, the efficient desymmetrization of *meso*-compounds, such as cyclic dicarboxylic acid **2** or its anhydride **3** into the (3a*S*,6a*R*)-lactone **6** still represents a major synthetic challenge,[2] and a number of investigations searching for a solution to this problem has been undertaken to date. However, the conversion of **2** to **6** *via* classical and enzymatic resolution involved multi-step reactions and resulted in poor overall yields.[3] Asymmetric hydrolysis of *meso*-diesters empolyed unavailable and very expensive polymer-supported PLE for chiral hemiesters,[4] albeit with excellent enantioselectivity. Enantioselective reduction of **3**[5] and its *meso*-cyclic *N*-benzylimide[6] relied upon the use of expensive Noyori's BINAL-H reducing agent and chiral oxazaborolidine catalysts in large quantities, respectively. The synthesis of **6** *via* a chiron approach required extensive and tedious column chromatographic purification in a multi-step synthetic effort starting from L-aspartic acid[7] and 4-formyl-3-mesyloxyazetidin-2-one.[8] A diastereoselective alcoholysis approach to diastereomeric hemiesters from **3** required stoichiometric quantities of the chiral nuclophile and additional chemical steps for its removal.[9] A different method for the desymmetrization of *meso*-cyclic anhydride has been achieved by employing catalytic asymmetric alcoholysis in the synthesis of biological active products.[10] Deng et al. realized the first modified bis-*Cinchona* alkaloid-catalyzed asymmetric methanolysis of **3** into the corresponding (4*R*,5*S*)-hemiester in excellent enantioselectivity (93% *ee*), as a key precursor for the formation of **6** to complete an asymmetric total synthesis of **1**.[11] In spite of the high enantioselectivity, its cryogenic conditions (−40 °C) and the use of a large excess of methanol as nucleophile rendered this synthetic route of limited application in industrial-scale synthesis. Therefore, the development of efficient and practical methods for the preparation of (3a*S*,6a*R*)-lactone **6** *via* a catalytic asymmertric alcoholysis under mild reaction conditions is still desirable in the synthesis of (+)-biotin.

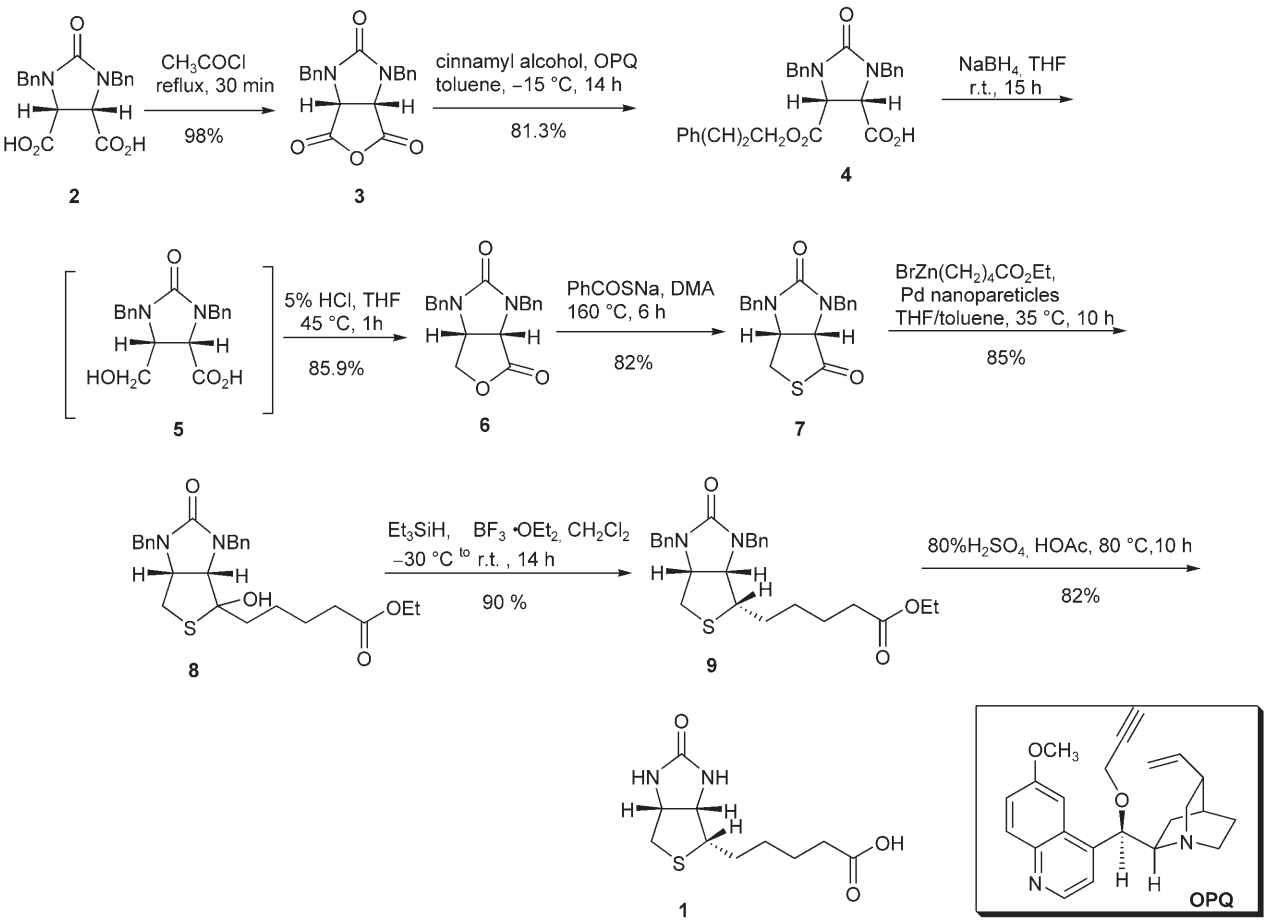
In recent years, the catalytic asymmetric alcoholysis of cyclic *meso*-anhydrides using only stoichometric cinnamyl alcohol as the nuclophile in the presence of quinine has been developed, which allowed the convenient enantioselective synthesis of the corresponding chiral cinnamyl hemiester with good to excellent enantioselectivity at a reaction temperature accepta-

ble for commercial-scale production.[12] These promising improvements have stimulated our efforts to develop a practical asymmetric total synthesis of (+)-biotin (**1**) *via* a highly enantioselective construction of (4*S*,5*R*)-cinnamyl hemiester **4** by the *Cinchona* alkaloid-mediated alcoholysis of **3** with cinnamyl alcohol under milder reaction conditions and introduction of the 4-carboxybutyl chain into **7** by an improved Fukuyama-type cross-coupling reaction[13] by employing palladium nanoparticles immobilized on anion exchange resin D296 (Pd@D296) catalyst as key steps.

Results and Discussion

Our synthetic route to **1** is depicted in Scheme 1. The *meso*-cyclic anhydride **3** was obtained in nearly quantitative yield by heating **2** with acetyl chloride at 50 °C for 30 min under solvent-free conditions.

With the *meso*-cyclic anhydride **3** in hand, our attention turned to the development of an efficient and practical asymmetric synthesis of **1** *via* the *Cinchona* alkaloid-mediated nuclophilic ring opening of **3** with cinnamyl alcohol. Initially, the asymmetric alcoholysis of **3** with 1.1 equiv. of *Cinchona* alkaloids (quinine and *O*-propargylquinine) in toluene at − 15 °C for 14 h was attempted; as expected, these reactions smoothly proceeded to afford the desired product in 96% and 97% yield with 87% *ee* and 88% *ee*, respectively (entries 1 and 3 in Table 1). Recrystallization of crude product **4** from AcOEt led to an enantiomer enrichment of ≥98% *ee*. The structure and absolute configuration of **4** was confirmed by its subsequent conversion into the known (3a*S*,6a*R*)-lactone **6** which was obtained by chemoselective reduction of the methyl ester group of the (4*S*,5*R*)-methyl hemiester with $LiBEt_3H$ followed by acid-catalyzed lactonization,[4b] and was further supported by an X-ray crystallographic analysis as shown in Figure 1. It is worth mentioning that these reactions were significantly slower, requiring 24 h at −15 °C to proceed to completion when quinine was used, compared to only 14 h at the same temperature for OPQ (entries 1 and 3 in Table 1). After the reaction was complete, these two *Cinchona* alkaloids could be easily be recovered almost quantitatively as their hydrochloride salts and, after basic work-up, be reused without any decrease of enantioselectivity in ten sequential reactions (en-



Scheme 1. The synthetic route to (+)-biotin (**1**).

Table 1. Investigation of the reaction conditions for the asymmetric desymmetrization of **3** with cinnamyl alcohol using *Cinchona* alkaloids.[a]

Entry	*Cinchona* alkaloid (equiv.)	Solvent	Temperature [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	QN (1.1)[d]	toluene	−15	24	96	87
2	QN(1.1)	toluene	−15	24	96	86.8[f]
3	OPQ (1.1)[e]	toluene	−15	14	97	88
4	OPQ (1.1)	toluene	−15	14	97	88.5[f]
5	OPQ (1.1)	toluene/CCl_4	−15	14	97	88
6	OPQ (1.1)	Et_2O	−15	14	93	78
7	OPQ (1.1)	THF	−15	14	93	74
8	OPQ (1.1)	CH_2Cl_2	−15	14	92	72
9	OPQ (90)	toluene	−15	14	95	87
10	OPQ (80)	toluene	−15	14	95	86
11	OPQ (70)	toluene	−15	14	95	79
12	OPQ (60)	toluene	−15	14	95	70
13	OPQ (80)	toluene	−50	42	95	91
14	OPQ (80)	toluene	−30	24	95	89
15	OPQ (80)	toluene	−5	10	95	70

[a] All reactions were performed with **3** (2 mmol) and cinnamyl alcohol (2.6 mmol).
[b] Isolated yield after column chromatography on silica gel using EtOAc/PE (10/1) as eluent.
[c] Determined by chiral HPLC stationary phase.
[d] QN = Quinine.
[e] OPQ = *O*-propargylquinine.
[f] The *Cinchona* alkaloid was recycled ten times.

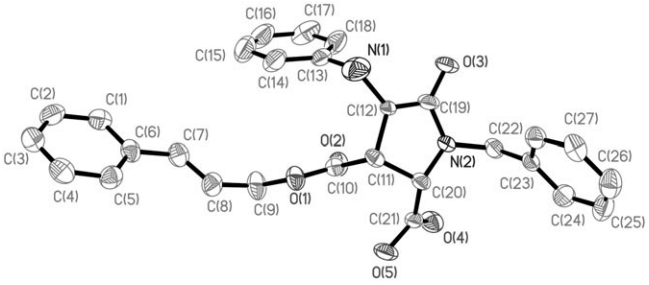


Figure 1. The structure and absolute configuration of **4.**

tries 2 and 4 in Table 1). Next, the reaction conditions were optimized with an investigation of the influence of the solvent, reaction temperature, and amount of OPQ on the yield and enantioselectivity of the alcoholysis of **3** with 1.3 equiv. of cinnamyl alcohol. The enantioselectivity of the desymmetrization of **3** are highly dependent on solvents. Low enantioselectivities were obtained with Et_2O, THF and CH_2Cl_2 (entries 6–8 in Table 1). A significant improvement in enantioselectivity, however, was achieved in toluene (entry 4 in Table 1). When using a solvent system consisting of toluene and CCl_4 in a 1:1 ratio, the enantioselective alcoholysis (entry 5 in Table 1) was almost the same as that in toluene. It is clear that toluene is the solvent of choice for this reaction. The enantioselectivity of **4** in reactions at −30 to −50 °C increased slightly as compared with the case at −15 °C (entries 14 and 13 in Table 1), the alcoholysis at −5 °C exhibited a significantly lower enantioselectivity (70% *ee*, entry 15 in Table 1) compared to the reaction at −15 °C, thereby precluding exploitation of further elevations of the reaction temperature. It is interesting to note that this desymmetrizition worked well even in the case of 0.8 equiv. of OPQ, high yield and enantioselectivity of **4** were obtained (entry 10 in Table 1), whereas reducing the amount of OPQ to 0.6 equiv. resulted in the lowest enantioselectivity (70% *ee*) (entry 12 in Table 1).

Chemoselective reduction of **4** was performed with $NaBH_4$ in THF at room temperature to afford the (4*S*,5*R*)-hydroxy acid **5** as the sodium salt after saponification with 10% aqueous Na_2CO_3, subsequent treatment with 5% aqueous HCl *via* acid-catalyzed lactonization afforded the key intermediate (3*aS*,6*aR*)-lactone **6** in 85.9% yield and 98% *ee*.

Thiolactonization of **6** was carried out by heating it with sodium benzothioate in *N,N*-dimethylacetamide at 160 °C for 6 h to provide (3*aS*,6*aR*)-thiolactone **7** in 82% yield. The by-product sodium benzoate formed in this reaction was recovered as benzoic acid after acid treatment in almost quantitative yield.

Next, we examined the possibility of the one-step installation of the 4-carboxybutyl chain onto 7 by employing palladium nanoparticles immobilized on anion exchange resin D296 (Pd@D296) as catalyst in a Fukuyama-type cross-coupling strategy.[13] Thus, the coupling of 7 with organozinc reagent, which was ob-

Table 2. Recycling of the catalyst in Fukuyama-type cross-coupling reaction in the preparation of **8** from **7**.[a]

Run	Reaction time[h]	Yield [%][b]
1	10	88
2	10.5	83.1
3	11	86.5
4	11.5	84.6
5	12	82.3

[a] *Reaction conditions:* compound **7** (1 mmol), organozinc reagent (2 mmol), Pd@D296 (0.01 mmol g^{-1}) in toluene/DMF (7/1) at 35 °C.

[b] Isolated yields after column chromatography on silica gel using EtOAc/PE (2/1) as eluent.

tained using the Huo procedure[14] from ethyl 5-bromopentanoate, was carried out in the presence of Pd@D296 ($d < 100$ nm, 0.01 mmol/g) at 35 °C in a mixture of THF and toluene for 12 h, As expected, this improved Fukuyama-type cross-coupling reaction proceeded well to provide the desired hydroxy ester **8** in 85% yield.

It is well-known that one of the advantages of polymer-immobilized palladium catalyst is its easy recovery by filtration.[15] The recycling of this catalyst was investigated by the coupling reaction of **7** with an organozinc reagent under the same reaction conditions as shown in Table 2.

As seen clearly from Table 2, the catalyst was recovered quantitatively by simple filtration and reused at least five times under the same reaction conditions. The catalytic activity and reaction rate were typically unaffected and the reactions were complete within 12 h even in the fifth consecutive run. Furthermore, it was comfirmed by TEM analysis that the palladium nanoparticles are still embedded in the anion exchang resin D296 support and no significant changes of the number and morphology in this catalyst are observed after the fifth reaction.

Ionic hydrogenation with triethylsilane is an effective method to reduce tertiary alcohols and has already been used in natural product synthesis.[16] The compound **8** was treated with triethylsilane and boron trifluoride etherate in CH_2Cl_2 at −30 °C to room temperature for 14 h, the hydroxy group at the C-4 postion was clearly reduced affording the desired (+)-dibenzyl biotin ester **9** as a single diastereoisomer in excellent yield, which was detected by integration of the ^{1}H NMR spectrum of the crude reaction product. The stereochemistry at C-4 for **9** was unambiguously assigned by means of ^{1}H-^{1}H NMR experiments. From the NOESY spectrum, the cross-peaks between C_{3a}-H/$C_{4\beta}$-H and the absence of Overhauser effects between C_{3a}-H/$C_{4\alpha}$-H indicated the α-orientation of the 4-carboxybutyl chain in **9** (Figure 2).

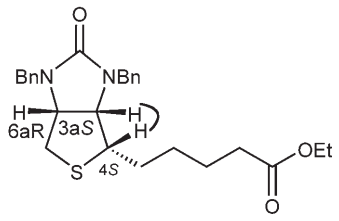


Figure 2. 2D NOESY interactions of compound **9**.

Finally, the compound **9**, upon a one-pot debenzylation-hydrolysis with 80% sulfonic acid and glacial acetic acid at 80 °C for 10 h, furnished the desired (+)-biotin (**1**) in 82% isolated yield.

Conclusions

In the current work, we have developed an efficient, enantioselective total synthesis of (+)-biotin in 35.2% overall yield starting from commercially available cyclic diacid **2**. The effective power of the catalytic enantioselective alcoholysis of *meso*-cyclic anhydride **3** into the chiral hemiester **4** using OPQ as organocatalyst and the palladium nanoparticles-catalyzed installation of 4-carboxybutyl chain in **7** *via* a Fukuyama-type cross-coupling process in the construction of the target molecule has been demonstrated. The short steps, simple operations and the use of all commercially available reagents, are all positive features that provide a very attractive technology for the industrial total synthesis of **1**.

Experimental Section

General Remarks

Reagents and chemicals were obtained from commercial suppliers and used without further purification. THF and toluene were dried with Na/benzophenone and stored over Na wire under N_2, CH_2Cl_2, Et_3N, DMF was distilled over CaH_2. Petroleum ether (PE) for column chromatography (CC) had a bp of 30–60 °C. Analytical TLC was carried out with silica gel GF254 plates (Qingdao, Haiyang, China). The Pd@D296 was prepared from a commercial anion exchange resin D296 (Tanjing, China) according to the literature.[17]

Melting points were measured with a WRS-1B digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-FT/IR-4200 spectrometer. NMR spectra were recorded on a Bruker Avance-400 spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) spectrometer with TMS as internal standard. Mass spectra were obtained on a Waters Quattro-Micromass instrument; electrospray ionization (ESI) technique; optical rotations were measured on a JASCO P-1020 digital polarimeter. HPLC: Agilent 1200.

cis-1,3-Dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (3)

A mixture of dicarboxylic acid **2** (3.54 g, 10 mmol) and acetyl chloride (5 mL, 70 mmol) was refluxed with stirring for 30 min, then evaporated under vacuum to give a crude product which was crystallized from toluene to give the pure **3** as a white powder; yield: 3.3 g (98%); mp 236.4–237.0 °C (Lit.[6a] mp 236–238 °C); IR (KBr): $\nu = 1805$, 1732, 1675, 1220 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.15$ (s, 2H), 4.18 (s, 2H), 4.22 (d, 1H, $J = 14.8$ Hz), 5.15 (d, 1H, $J = 14.8$ Hz), 7.15–7.35 (m, 10 H); MS (ESI): $m/z = 337.4$ ($M^+ + 1$, calcd.: 336.3).

(4*S*,5*R*)-1, 3-Dibenzyl-2-oxo-5-[(3-phenylallyloxy)-carbonyl]imidazolidine-4-carboxylic Acid (4)

To a stirred solution of **3** (4.80 g, 14.2 mmol) and OPQ (4.13 g, 11.4 mmol) in toluene (200 mL) was added dropwise a solution of cinnamyl alcohol (2.47 g, 18.5 mmol) in toluene (50 mL) at −15 °C over a period of 2 h under an N_2 atmosphere, and the stirring was continued for 12 h at this temperature. Then the mixture was allowed to warm to 0 °C and was washed with 1.2 M HCl (3 × 40 mL) and H_2O (50 mL). The aqueous phase was collected. The organic layers were washed with saturated aqueous NaCl (3 × 25 mL), and H_2O (3 × 25 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE, 10/1) to give **4** as colorless crystals; yield: 6.35 g (95%, 86% *ee*); Recrystallization from AcOEt gave the pure **4** as colorless crystals; yield: 5.43 g (81.3%, ≥98% *ee*). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD-H, hexane/IPA/AcOH = 88/10/2, $\lambda = 280$ nm, 0.5 mL min^{-1}): (−)-**4** = 36.7 min, (+)-**4** = 43.9 min; mp 122.0–122.8 °C, $[\alpha]_D^{21.9}$: +7.58 (*c* 1, MeOH); IR (KBr): $\nu = 3449$, 3028, 2930, 1751, 1711, 1664, 1450, 1357, 1238, 1196, 748, 701 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.02$–4.13 (m, 4 H), 4.62–4.72 (m, 2 H), 5.01 (d, $J = 14.8$ Hz, 1H), 5.09 (d, $J = 14.8$ Hz, 1H), 6.13–6.21 (dt, $J = 16.0$, 6.4 Hz, 1H), 6.59 (d, $J = 16.0$ Hz, 1H), 7.18–7.39 (m,15 H), 10.53 (br s, 1H). MS (ESI): $m/z = 470.3$ (M^+, calcd.: 470.5).

To recover the catalyst OPQ, 2N aqueous NaOH was added to the aqueous phase to adjust the solution to a pH value of 12. The resulting mixture was extracted with EtOAc (3 × 50 mL), and the organic layer was washed with saturated aqueous NaCl (3 × 25 mL) and H_2O (3 × 25 mL), dried over Na_2SO_4 and concentrated to give the catalyst as an off-white solid in almost quantitative recovery. The recovered catalyst was used in the reaction a new batch of substrates to give **4** in the same *ee* and yield as described above.

(3a*S*,6a*R*)-1,3-Dibenzyl-tetrahydro-1*H*-furo[3,4-*d*]imidazole-2, 4-dione(6)

To a stirred suspension of $NaBH_4$ (0.76 g, 20 mmol) in THF was added dropwise compound **4** (4.70 g, 10 mmol) in THF (50 mL) at 0 °C. The stirring was continued for 30 min at the same temperature, the reaction mixture was allowed to warm up to room temperature and stirred for further 15 h. After evaporation under vacuum, the residue was subsequently exposed to EtOAc (50 mL) and washed with 10% aqueous Na_2CO_3 (3 × 20 mL), the combined aqueous phases were neutralized with 35% aqueous HCl, then 5% aqueous HCl (40 mL) and EtOH (30 mL) were added to the reaction mixture. After stirring at 45 °C for 1 h and the resulting mixture was extracted with EtOAc (4 × 50 mL) at room temperature. The combined organic layers were washed with saturated aqueous NaCl (3 × 20 mL) and H_2O (3 × 20 mL), dried over Na_2SO_4 and concentrated to give **6** as a white crystalline powder; yield: 2.77 g (85.9%, *ee* ≥98%); The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD-H, hexane/IPA/AcOH = 70/30, $\lambda =$ 210 nm, 0.5 mL min^{-1}); mp 119.6–121.2 °C, $[\alpha]_D^{25}$: + 62.0 (*c* 2.0, $CHCl_3$) {Lit.[6d] mp 117–119 °C; $[\alpha]_D^{25}$: + 59.3° (*c* 1.0, $CHCl_3$)}; IR (KBr): $\nu = 1782$, 1690, 1420, 1211 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 3.92$ (d, 1H, $J = 12.0$ Hz), 4.09–4.15 (m, 3H), 4.34, 4.38 (2d, 2H, $J = 8.0$, 8.0 Hz), 4.62 (d, H, $J =$ 16.0 Hz), 5.04 (d, H, $J = 12.0$ Hz), 7.24–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$): $\delta = 45.2$, 416.9, 52.4, 54.4, 70.1, 76.7, 77.0, 77.3, 127.9, 128.0, 128.2, 128.8, 128.9, 129.1, 136.0, 158.2, 172.8; MS (ESI): $m/z = 345.2$ ($M + Na^+$, calcd.: 345.2).

(3a*S*,6a*R*)-1,3-Dibenzyltetrahydro-1*H*-thieno[3,4-*d*]-imidazole-2,4-dione (7)

A mixture of **6** (3.22 g, 10 mmol), sodium benzothioate (2.0 g, 12 mmol, 96%) and DMA (50 mL) was stirred at 160 °C for 6 h under an N_2 atmosphere. The solvent was removed under reduced pressure and the residue cooled to room temperature. H_2O (50 mL) and toluene (30 mL) were added to the reaction residue. The organic layer was separated and the aqueous phases were extracted with toluene (3 × 25 mL). The combined organic extracts were washed successively with saturated aqueous NaCl (3 × 25 mL) and H_2O (4 × 25 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give the crude product, which was recrystallized from EtOAc to afford the pure **7** as a white crystalline powder; yield: 2.77 g (82%); mp:125.2–126.4 °C; $[\alpha]_D^{20}$: + 90.2 (*c* 1.0, $CHCl_3$); {Lit.[5b] mp 125–127 °C; $[\alpha]_D^{20}$: +89.5(*c* 1.0, $CHCl_3$)}; IR (KBr): $\nu = 1712$, 1689, 1415, 1219 cm^{-1}; ^1H NMR ($CDCl_3$); $\delta = 3.30$ (dd, 1H, $J = 4.0$, 1.6 Hz), 3.38 (dd, 1H, $J = 4.0$, 8.0 Hz), 3.84 (d, 1H, $J =$ 8.0 Hz), 4.14–4.18 (m, 1H), 4.36, 4.40 (dd, 2H, $J = 4.0$, 4.0 Hz), 4.70 (d, H, $J = 12.2$ Hz), 5.06 (d, H, $J = 12.2$ Hz), 7.29–7.40 (m, 10H); MS (ESI): $m/z = 361.0$ ($M + Na^+$, calcd.: 361.3).

To recover the by-product, 6N aqueous HCl was added to the aqueous layer to adjust the solution to a pH value of 1–2, and the solution was kept in a refrigerator overnight to afford benzoic acid as colorless crystals; yield: 1.4 g (98%).

Ethyl 5-{(3a*S*,6a*R*)-1,3-Dibenzyl-4-hydroxy-2-oxo-hexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl}-pentanoate (8)

To a suspension of zinc dust (1.6 g, 24.6 mmol) in THF (3 mL) and toluene (2 mL) was added iodine (0.16 g, 1.23 mmol) at room temperature then the mixture was warmed to 50 °C. Ethyl 5-bromopentanoate (2.6 g, 12.4 mmol) was added dropwise over a period of 30 min. The reaction mixture was stirred for 2 h at same temperature and cooled to 30 °C, **7** (2.1 g, 6.2 mmol) and Pd@D296 (0.65 g, 0.065 mmol) in toluene/DMF (7/1, 6 mL) were added. After stirring at 35 °C for 10 h, H_2O (5 mL) was added. The mixture was filtered after stirring for 20 min.

The organic phase was collected and the aqueous layer was extracted with toluene (3×10 mL). The combined organic extracts were washed successively with H_2O (2×10 mL) and saturated aqueous NaCl (3×10 mL), dried over Na_2SO_4, and evaporated under vacuum to afford the crude product **8**, which was purified by column chromatography on silica gel using EtOAc/PE (2/1) to afford the pure **8** as a yellow oil; yield: 2.47 g (85%); $[\alpha]_D^{20}$: +20.9 (*c* 1.0, $CHCl_3$); IR (KBr): ν=2961, 2594, 1670, 1387, 1259, 665 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.23–1.27 (m, 3 H), 1.44–1.45 (m, 2 H), 1.60–1.62 (m, 2 H), 2.24–2.33 (m, 4H), 2.72 (m, 2H), 3.65 (m, 1H), 3.94 (d, 1H, *J*=22.4 Hz), 4.02 (d, 1H, *J*=22.4 Hz), 4.10–4.20 (m, 4H), 4.88 (d, 1H, *J*=15.6 Hz), 5.10 (d, 1H, *J*=15.6 Hz), 7.24–7.32 (m, 10 H). MS (ESI): *m*/*z*=469.4 (M^++1, calcd.: 469.6).

Ethyl 5-{(3a*S*,4*S*,6a*R*)-1,3-Dibenzyl-2-oxo-hexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl}-pentanoate (9)

To a solution of **8** (0.75 g, 1.6 mmol) and triethylsilane (1.3 mL, 16 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise freshly distilled $BF_3{\cdot}OEt_2$ (1.0 mL, 8 mmol). The reaction mixture was stirred at −30 °C for 4 h, allowed to warm to room temperature and further stirred for 10 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (3×10 mL), dried over $MgSO_4$ and evaporated under vacuum to afford the crude product **9**, which was purified by column chromatography on silica gel using EtOAc/PE (1/1) to afford the pure **9** as colorless crystals; yield: 0.65 g, (90%); mp 73.6–74.4 °C, $[\alpha]_D^{21.9}$: −24.9 (*c* 1, MeOH); IR (KBr) : ν=1728, 1678, 1453, 1243, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ=1.25–1.28 (t, 3H, *J*=8 Hz), 1.57–1.65 (m, 6H), 2.27–2.31 (t, 2H, *J*=7.2 Hz), 2.68, 2.72 (dddd, 2H, *J*=5.6 Hz, *J*=5.6 Hz), 3.05 (m, 1H), 3.86–4.12 (m, 6H), 4.72 (d, 1H, *J*=15.2 Hz), 5.05 (d, 1H, *J*=15.2 Hz),7.23–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$): δ=173.6, 161.1, 137.0, 136.9, 128.7, 128.3, 127.3, 62.6, 61.2, 60.3, 54.3, 48.0, 46.6, 34.8, 34.2, 28.7, 28.5, 24.7, 14.3; MS (ESI): *m*/*z*=453.3 (M^++1, calcd.: 453.6).

(+)-Biotin (1)

To a stirred suspension of **9** (4.53 g, 10 mol) and acetic acid (50 mL), was added 80% H_2SO_4 (150 mL) dropwise at room temperature over a period of 25 min. The reaction mixture was stirred at 80 °C for 10 h. After cooling to room temperature, H_2O (100 mL) was added. The reaction mixture was extracted with toluene (4×65 mL) at 60 °C. The aqueous phase was concentrated under reduced pressure to approximately a volume of 120 mL and kept in a refrigerator overnight. The precipitate was collected by filtration and recrystallized from H_2O to give pure **1** as a white crystalline powder; yield: 2.0 g (82%); mp 231–232 °C; $[\alpha]_D^{21.9}$: +91.0 (*c* 1, 0.1 M NaOH); {Lit.[5b] mp 232–233 °C; $[\alpha]_D^{20}$: +91.2° (*c* 1.0, 0.1 N NaOH)}; IR (KBr): ν=3316, 2943, 1715, 1663; ^1H NMR ($CDCl_3$): δ=1.30–1.65 (m, 6H), 2.21 (t, 2H, *J*=7.3 Hz), 2.65 (dd, 1H, *J*=1.7, 12.5 Hz), 2.83 (dd, 1H, *J*=4.7, 12.5 Hz), 3.09–3.17 (m, 1H), 4.09–4.15 (m, 1H), 4.29–4.32 (m, 1H), 6.35 (s, 1H), 6.43 (s, 1H), 11.98 (br s, 1H). MS (ESI): *m*/*z*=245.4 (M^+, calcd.: 244.3).

X-Ray Crystallographic Study

The data were collected at room temperature on a Bruker Smart APEX diffractometer equipped with a normal focus, 2.4 kW sealed tube X-ray source (Mo Kα radiation, λ=0.71073 Å) operating at 50 kV and 30 mA. A hemisphere of intensity data was collected with a scan width of 0.60° in ω and exposure time of 10 s per frame. An empirical absorption corrections based on the SADABS program was applied for both compounds. The structure was solved by direct method followed by successive difference Fourier methods. All calculations were performed using SHELXS and SHELXTL-97.[18] Crystal data for compound **4:** $C_{28}H_{26}N_2O_5$, M=470.52, monoclinic, *P*2/*n*, *a*=7.971(6) Å, *b*=10.656(9) Å, *c*=28.58(2) Å; β=104.87(4)° *Z*=4; *V*=2428(3) $Å^3$, $\rho_{calcd.}$=1.285 $g\,cm^{-3}$. Data were collected on a single crystal with dimensions 0.15×0.08×0.08 mm^3. 11177 reflections were measured, in the range of $1.42 \le \theta \le 26.00$ ($-9 \le h \le 8$, $-13 \le k \le 11$, $-35 \le l \le 34$), 4736 independent reflections (R_{int}=0.0416). Final R_1=0.0669 [$I > 2\sigma(I)$], wR_2=0.1565, and the goodness-of-fit on F^2 is 1.044. 687835

CCDC 687835 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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