Synthetic Studies on *d*-Biotin, Part 8:[1] An Efficient Chemoenzymatic Approach to the Asymmetric Total Synthesis of *d*-Biotin *via* a Polymer-Supported PLE-Mediated Desymmetrization of *meso*-Symmetic Dicarboxylic Esters

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Received: October 11, 2004; Accepted: January 3, 2005

Dedicated to Prof. Yuguo Zhong on the occasion of his 70th birthday and his retirement.

Abstract: A practical chemoenzymatic method for the asymmetric total synthesis of *d*-biotin (**1**) starting from the commercially available *cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (**2**) has been developed. The key step of the synthesis is the highly enantioselective hydrolysis of *meso*-dicarboxylic esters by a polymer-supported pig liver esterase and introduction of a formyl group at the C-4 position in **4** *via* a Grignard reaction. The polymer-supported PLE can be recovered quantitatively from the reaction mixture by simple filtration and reused without significant loss of activity.

Keywords: *d*-biotin; desymmetrization; enzyme catalysis; kinetic resolution; polymer-supported PLE; vitamin H

Introduction

Although marked advances in the total synthesis of *d*-biotin (**1**) in the last 55 years have been achieved,[2] the 1949 Goldberg and Sternbach 14-step approach, utilizing (3*aS*, 6*aR*)-thiolactone **6** as a key intermediate, is still relevant today, with minor improvements, for large-scale syntheses.[3] The undesirability of involving an intermediate resolution progress, which required the recycling of a large amount of resolving agents in the preparation of the chiral building block, (3a*S*, 6a*R*)-lactone **5**, has provided an impetus to search for alternatives. For example, Matsuki's group reported[4] the example of a one-pot enantioselective reduction of the *meso*-anhydride of **2** to **5** with 90% ee. However, this approach required the use of a large excess of Noyori's BINAL-H complexes. Choi et al.[5] have reported a catalytic asymmetric synthesis of **5** with modified *Cinchona* alkaloids *via* enantioselective methanolysis of the *meso*-anhydride of **2** and a one-pot chemoselective reduction with high enantioselectivity (90% ee). But this method required the very expensive dihydroquinidine phenanthryl ether (DHQD-PHN) as catalyst. Very recently, we reported the enantioselective reduction of the *meso*-cyclic imide into hydroxylactam as a key chiral building block to prepare **5** in excellent yield and enantiomeric excess ($\geqslant$ 98%) in the presence of chiral oxazaborolidine catalyst[1] or polymer-supported chiral oxazaborolidine catalyst.[6] The chromatographic purification of the chiral hydroxylactam was needed, thus making the two approaches very difficult for large-scale synthesis. As a result, the development of efficient and practical methods that exhibit high enantioselectivity is still a highly desirable yet exclusive goal in the asymmetric synthesis of *d*-biotin.

In a wide variety of asymmetric methods, enzymatic asymmetric hydrolysis has become a very powerful method in the development of strategies for the asymmetric synthesis of various natural products.[7] In particular, esterases, such as pig liver esterase (PLE), are now widely used in asymmetric organic synthesis, notably in the desymmetrization of *meso* compounds.[8] In this way, prochiral diesters can be hydrolyzed to enantiomerically enriched hemiesters in up to quantitative yield.[9] In 1982, Iriuchijima and co-workers[10] realized the first PLE-catalyzed asymmetric hydrolysis of prochiral diesters **3** into the corresponding (4*S*,5*R*)-hemiester **4** as a precursor for the formation of (3a*S*,6a*R*)-lactone **5** to perform an asymmetric total synthesis of **1**. However, the efficiency of biocatalyst recovery and recycling becomes a critical feature for the economical viability of an industrial process based on such an enzyme. There-

 DOI: 10.1002/adsc.200404311

fore, a practical means of separating the biocatalyst before work-up has to be devised. Obviously, immobilization of PLE would offer a solution to this problem.

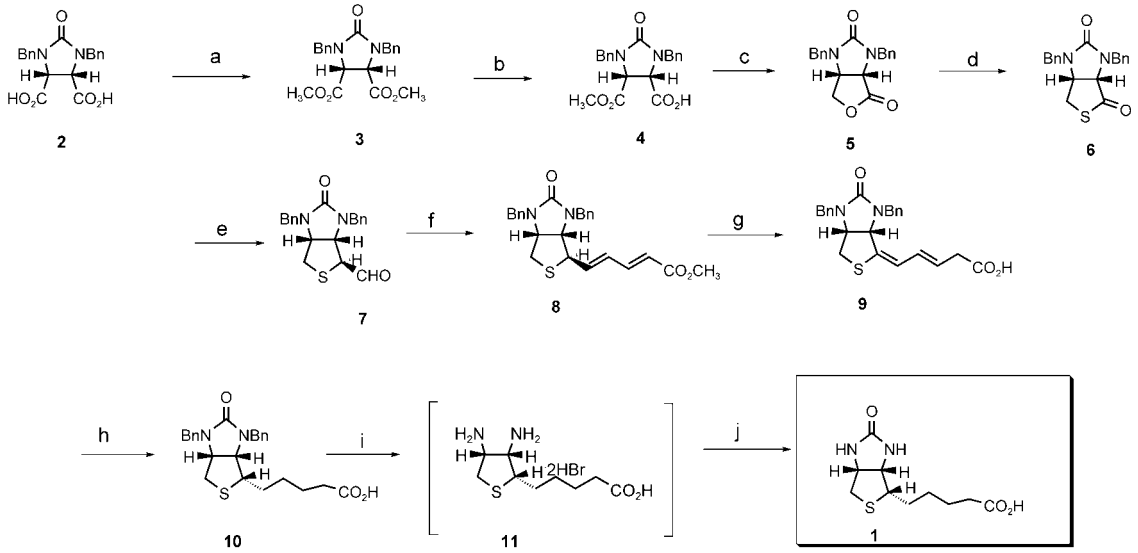
In continuation of our continued interest in developing new and practical routes for the total synthesis of **1**, we to report herein an efficient and more economical method for the asymmetric synthesis of **1**, which involves the polymer-supported PLE-catalyzed hydrolysis of **3** into the (4*S*,5*R*)-hemiester **4** and the assembly of the formyl group at the C-4 position in (3a*S*,6a*R*)-thiolactone **6** *via* a Grignard reaction.

Results and Discussion

The present synthetic route to **1** is outlined in Scheme 1. The known *meso*-dicarboxylic diester **3** was prepared in 95% yield by heating commercially available *cis*-1,3-dibenzyl-2-imidazoidione-4,5-dicarboxylic acid (**2**) and methanol in benzene with a catalytic amount of H_2SO_4 with azeotropic removal of water.

With the prochiral *meso*-dicarboxylic diesters **2** in hand, the next crucial step of our approach to **1** was the enantioselective hydrolysis of **3** into the (4*S*,5*R*)-hemiester **4** with the immobilized PLE on Eupergit C®.[11] The reaction was conducted in 0.1 M aqueous phosphate buffer suspensions at 30 °C for 45 h, which were adjusted and kept constant at pH 8 by the continuous addition of 1 M aqueous NaOH using a pH stat. As expected, the (4*S*,5*R*)-hemiester **4** was achieved in a yield of 90% with an enantiomeric excess of 91%, which was then upgraded to ≥98.5% ee by recrystallization from toluene. The enantiomeric purity of **4** was determined by chiral HPLC and ^{1}H NMR analysis of the diastereoisomers of (*S*)-1-(1-naphthyl)-ethylamine obtained by treatment of **4** with (*S*)-1-(1-naphthyl)-ethylamine according to the literature procedure.[8c] The absolute configuration of **4** (CCDC no. 249374) was verified by X-ray diffraction analysis (Figure 1). Significantly, after the asymmetric hydrolysis was completed, the polymer-supported PLE used could be conveniently recovered from the reaction mixture by simple filtration followed by washing with 0.1 M aqueous phosphate buffer.

One of the most useful features of polymer-supported enzyme catalyst is its ability to be recycled.[12] To show that the immobilized PLE can be recycled for a number of times, the hydrolysis of **3** using the polymer-supported PLE was repeated four times. As shown in Table 1, the enzyme-catalyzed hydrolysis proceeded smoothly without any decrease of the enantiomeric excess of **4** in every cycle, clearly indicating the reusability of the polymeric enzyme without loss of catalytic performance. Also, the rate of hydrolysis was increased with each successive cycle of the enzyme. This reaction went to completion within 45 h when the enzyme was first employed. Only 36 h in the second cycle (entry 2) and 29 h in the third cycle (entry 3). Complete conversion in the fourth cycle was observed after only 25 h (entry 4). This may be ow-



Scheme 1. Synthetic scheme for the total synthesis of *d*-biotin (**1**). *Reaction conditions*: a) CH_3OH, H_2SO_4, benzene, reflux, 6 h, 95%; b) polymer-supported PLE, 0.1 M aqueous phosphate, 0.1 M aqueous NaOH, pH 8, 45 h, 30 °C, then 1 M aqueous HCl, 90%; c) $LiEt_3BH$, THF, 0 °C to r.t., 6 h, then 1 M aqueous HCl, 45 °C, 1 h, 88%; d) EtOC(S)SK, DMA, 125 °C, 7 h, 70%; e) CH_3OCH_2MgI, *n*-Bu_2O, toluene, 45 °C to 15 °C, 3 h, then 0 °C to r.t., 1 M aqueous HCl, reflux, 3 h, 78%; f) $(EtO)_2P(O)CH_2$-$CH{=}CHCO_2CH_3$, $Ba(OH)_2 \cdot 0.8\ H_2O$, dioxane, H_2O, 70 °C, 2.5 h, 90%; g) 1 M aqueous KOH, CH_3OH, *n*-Bu_4NBr, r.t., 8 h, then 1 M aqueous HCl; h) H_2, $Pd(OH)_2$/C, AcOEt, 10 atm, 15 h, r.t., 82% (from **8** to **10**); i) 47% aqueous HBr, reflux, 42 h; j) (i) diphosgene, 3 M aqueous KOH, *n*-Bu_4NBr, toluene, r.t., 6.5 h; (ii) 2 M aqueous HCl, 82% (from **10** to **1**).

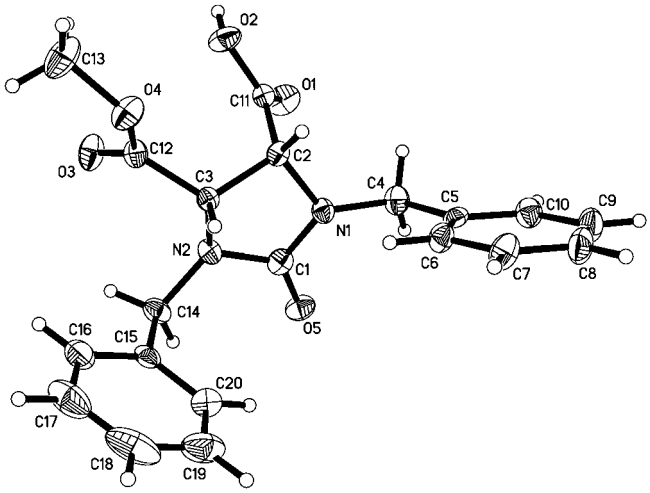


Figure 1. Molecular structure of (4*S*,5*R*)-hemiester **4** (CCDC No. 249374) in the crystal. The thermal ellipsoids are drawn at the 30% probability level.

ing to a preadjustment of the conformation of the enzyme by incorporation of water molecules after catalytic hydrolysis.

Chemoselective reduction of the ester group of **4** with super-hydride ($LiEt_3BH$) in THF at room temperature for 2.5 hours, followed by acid-catalyzed lactonization afforded (3a*S*,6a*R*)-lactone **5** in 88% yield with 96.5% enantiomeric excess. The lactone was increased up to $\geqslant$99% ee by recrystallization from ethanol, which was treated with potassium *O*-ethyl dithiocarbonate [EtOC(S)SK] in anhydrous *N,N*-dimethylacetamide (DMA) at 125 °C for 7 hours to provide the desired (3a*S*,6a*R*)-thiolactone **6** in 80% yield.

The introduction of the formyl group was carried out by the addition of the Grignard reagent, derived from iodomethyl methyl ether[13] and magnesium, to **6** in *n*-Bu_2O/toluene (1:1) at 15 °C and subsequent treatment with 1 M aqueous HCl at reflux *via* dehydration/hydrolysis in a one-pot procedure to afford the (3a*S*,4*R*,6a*R*)-aldehyde **7** exclusively in 78% yield. It should be noted that the Grignard reaction of **6** is dependent upon the reaction solvent. In THF, the yield of **7** was 45%, but the use of ether considerably improved the yield to 63%. The stereochemistry of (3a*S*,4*R*,6a*R*)-aldehyde **7** was obvious from the lack of vicinal coupling between the protons α and β to the aldehyde, clearly indicating that C-4–Ha and C-3–Ha are *anti*-disposed, and a β-orientation of the hydroxy group at C-4 in **7**.

The Horner–Emmons reaction of **7** in dioxane at 70 °C with diethyl 3-methoxycarbonyl-2-propenylidine phosphonate using activated barium hydroxide catalyst C-200 [$Ba(OH)_2 \cdot 0.8\ H_2O$][14] under interfacial solid-liquid conditions following Sinisterra's conditions provided the (*E,E*)-2,4-dienyl ester **8** in 90% yield as a single isomer. Comparison of the ^1H and ^{13} CNMR data of **8** with literature data[15] revealed that the (*E,E*)-2,4-dienyl ester **8** was the only product of this reaction. Treatment of **8** with potassium hydroxide in methanol in the presence of *n*-Bu_4NBr (TBAB) effected a one-step transformation involving the positional isomerization of the conjugated double bond of 5-side chain, hydrolysis and acidification. The resulting crude 3,5-dienyl acid **9** upon hydrogenation in ethyl acetate at 30 °C and 10 atm of H_2 using $Pd(OH)_2$/C catalyst led stereospecifically to dibenzyl-biotin **10** in 82% yield based on **8**.

Finally, transformation of **10** into **1** was performed in three steps in a similar way to our previous procedure.[6] Heating **10** with 47% aqueous HBr at reflux for 42 hours *via* a one-pot debenzylation and ring opening reaction gave rise to the diamine·2 HBr salt. Non-purified **11** was subjected to the phase-transfer-catalyzed ring closing reaction upon treatment with diphosgene in the presence of 3 M aqueous KOH and a catalytic amount of TBAB in toluene at room temperature for 6.5 hours to afford the desired *d*-biotin (**1**) in 82% yield

Table 1. Recycling of polymer-supported PLE in the asymmetric hydrolysis of **3** in 0.1 M aqueous phosphate buffer at 30 °C.

Run	Reaction time [h]	Yield [%][a]	ee [%][b]
1	45	90	91
2	36	90.5	91
3	29	91	90.5
4	25	90	91

[a] Yields refer to crude products

[b] Determined by HPLC analysis of the diastereomeric (*S*)-1-(1-naphthyl)ethylamides prepared from **4** and (*S*)-1-(1-naphthyl)ethylamine, using a Daicel column (Chiralpak OD, hexane/*i*-PrOH, 4:1).

Conclusion

In summary, we have developed an efficient synthesis of *d*-biotin (**1**) starting from readily accessible *cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid in about 25% overall yield. Notable features include the enzymatic desymmetrization of *meso*-dicarboxylic esters **3** with polymer- supported PLE to prepare the key chiral (4*S*,5*R*)-monoester **4** and introduction of a formyl group in **4** *via* a modified Grignard reaction. This procedure should permit the practical large-scale preparation of *d*-biotin.

Experimental Section

General Remarks

Commercially available reagents were used as received. DMA was distilled over CaH_2 and stored under N_2 over 3 Å mo-

lecular sieves. THF, *n*-Bu_2O and toluene were dried with Na/benzophenone and stored over Na wire under N_2. Iododimethyl methyl ether[13] was prepared through the treatment of an excess of the dimethyl acetal of formaldehyde with trimethylsilyl iodide. Polymer-supported PLE[11] and C-200 catalyst[14] were prepared according to the literature procedures. Analytical TLC was carried out with silica gel GF254 plates (Qingdao, Haiyang, China).

Melting points were measured with a WRS-1 digital melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FI-IR 300 spectrometer. NMR spectra were recorded on a Bruker AMX 300 (^{1}H NMR: 300 MHz, ^{13}C: 100 MHz) spectrometer with TMS as internal standard. Mass spectra were obtained on an HP-5988A spectrometer by direct inlet at 70 eV. Optical reactions were measured on a Perkin-Elmer 241 MC polarimeter

Dimethyl *cis*-1,3-Dibenzyl-2-imidazolidine-4,5-dicarboxyate (3)

A mixture of **2** (283.2 g, 0.8 mol), CH_3OH (162 mL, 4 mol), conc. H_2SO_4 (4 mL, 75.1 mmol), and benzene (650 mL) was stirred at reflux using a Dean–Stark apparatus for 6 h. After the removal of solvent under vacuum, the residue was diluted with H_2O (400 mL) and EtOAc (400 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×100 mL). The combined organic layers were washed with 2 M Na_2CO_3 (3×50 mL) and H_2O (4×50 mL), dried over (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was recrystallized from CH_3OH to afford the pure **3** as a white crystalline powder; yield: 290.3 g (95%); mp 111–112 °C (Lit.[10] mp 109–112 °C); IR (KBr): $\nu=1749, 1735, 1700$ cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=3.65$ (s, 6H), 4.07 (d, 4H, $J=14.75$ Hz), 4.98 (d, 2H, $J=14.95$ Hz), 7.20–7.30 (10H); MS (EI): *m/z* (%) = 382 (M^+, 7.62), 325 (1.1), 264 (1.8), 291 (11), 91 (100).

(4*S*,5*R*)-1, 3-Dibenzyl-5-(methoxycarbonyl)-2-oxo-imidazolidine-4-carboxylic Acid (4)

To a suspension of **3** (19.1 g, 50 mmol) in a mixture of 0.1 M phosphate buffer (pH 8, 1.0 L) and CH_3OH (800 mL) was added polymer-supported PLE (408 units, 6.0 mg). The reaction mixture was stirred at 30 °C for 45 h. The pH value of reaction mixture was kept at 8 by addition of 1 M NaOH. The reaction was stopped by adjusting the pH to 9. The polymeric-supported PLE catalyst was filtered and washed several times with 0.1 M phosphate buffer and stored in a buffer suspension for reuse. The combined aqueous layer was acidified to pH 2.0 with 1 M HCl and extracted with EtOAc (4×150 mL). The combined organic layers were washed with H_2O (3×100 mL) and saturated aqueous NaCl (3×80 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give the crude **4** as a white solid; yield: 16.6 g (90%), mp 145–148 °C, $[\alpha]_D^{25}$: +6.68° (*c* 1.0, DMF). Recrystallization from toluene afforded pure **4** as a white crystalline powder; yield: 14.7 g (80%); mp 150–151 °C, $[\alpha]_D^{25}$: +7.31 (*c* 1.0, DMF) {Lit.[16] mp 149–150 °C, $[\alpha]_D^{20}$: −27.6 (*c* 1.0, DMF)}; IR (KBr): ν =3257, 1963, 1706, 1450, 1256, 1237, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=3.54$ (s, 3H), 4.00–4.15 (m, 4H), 4.66 (d, 1H, $J=15.4$ Hz), 4.77 (d, 1H, $J=15.4$), 7.19–7.36 (m, 10H), 13.4 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=46.8, 47.1, 53, 56.8, 57, 57.5, 128, 128.8, 128.96, 129.02, 135.7, 159.8, 168.8, 171$; MS (EI): *m/z* (%) = 368 (M^+, 3), 3336 (10), 323 (4), 309 (7), 277 (2.6), 264 (9.4), 134 (6), 91 (100), 65 (12).

(3a*S*,6a*R*)-1, 3-Dibenzyltetrahydro-4*H*-furo[3,4-*d*]-imidazole-2,4(1*H*)-dione (5)

To a stirring solution of **4** (17.2 g, 45 mmol) in THF (280 mL) was added dropwise $LiEt_3BH$ (1.0 M in 155 mL THF, 155 mmol) at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was allowed to warm up to room temperature, and stirred for 5.5 h, monitoring the reaction by TLC. Then 1 M aqueous HCl (200 mL) was added with stirring at 45 °C for 1 h. After cooling to room temperature, the resulting mixture was extracted with EtOAc ($4\times$ 55 mL). The combined organic layers were washed with saturated aqueous NaCl (3×400 mL) and H_2O (3×400 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by recrystallization from EtOH to afford pure **5** as a white crystalline powder; yield: 12.75 g (88%); mp 119–121 °C; $[\alpha]_D^{25}$: +61.3 (*c* 2.0, $CHCl_3$) {Lit.[1] mp 120–121 °C; $[\alpha]_D^{25}$: +61.5 ^{0} (*c* 2.0, $CHCl_3$)}; IR (KBr): $\nu=1785, 1704, 1416, 1210$ cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=3.59$ (s, 3H), 4.03–4.14 (m, 4H), 4.97 (d, 1H, $J=$ 14.8 Hz). 5.07 (d, 1H, $J=14.8$ Hz). 7.20–7.40 (m, 10H), 10.52 (br s, 1H);^{13}C NMR ($CDCl_3$): $\delta=45.5, 47.1, 53, 54.6, 70.2, 128.1, 128.3, 128.4, 128.9, 129, 129.1 136.1, 136.2, 158.4$; MS (EI): *m/z* (%) = 322 (M^+, 24.5), 264 (6.91), 231 (6.94), 187 (16.1), 91 (100).

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

A stirred mixture of **5** (19.3 g, 60 mmol), potassium *O*-ethyl dithiocarbonate (11.5 g, 72 mmol) and DMA (130 mL) was heated at 125 °C for 7 h under N_2. The reaction mixture was cooled to room temperature and diluted with H_2O (120 mL) and toluene (180 mL). The organic layer was separated and the aqueous layer was extracted with toluene (3×30 mL). The combined organic layers were washed with saturated aqueous NaCl (3×45 mL) and H_2O (4×30 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give the crude product which was purified by recrystallization from EtOAc to afford the pure **6**; yield: 16.2 g (80%); mp125–126 °C; $[\alpha]_D^{20}$: +90.2 (*c* 1.0, $CHCl_3$) {Lit.[17] mp 125–127 °C; $[\alpha]_D^{20}$: +90.8 (*c* 1.0, $CHCl_3$)}; IR (KBr): $\nu=1705, 1694, 1425, 1226$ cm^{-1}; ^{1}H NMR ($CDCl_3$); $\delta=3.27$ (dd. 1H, $J=2.2$, 12.8 Hz), 3.38 (dd, 1H, $J=5.5$, 12.8 Hz), 3.80 (d, 1H, $J=8.1$ Hz), 4.13 (ddd, 1H, $J=2.2$, 5.5, 8.1 Hz), 4.35, 4.36, 4.68, 5.04 (4×d, 4H, J =15.2 Hz), 7.28–7.335 (m, 10H); MS (EI): *m/z* (%) = 338 (M^+, 17), 310 (23), 277 (9), 264 (65).

(3a*S*,4*R*,6a*R*)-1,3-Dibenzyl-4-formyl-1*H*-tetrahydrothieno[3,4-*d*]imidazole-2(3*H*)-one (7)

Iodomethyl methyl ether (3.44 g, 20 mmol) was added to a stirred suspension of magnesium (6.32 g, 0.26 mol) in a mixture *n*-

Bu_2O (35 mL) and toluene (35 mL) at 45 °C under a nitrogen atmosphere, when reaction has started, the remaining iodomethyl methyl ether (41.3 g, 0.24 mol) in a mixture of *n*-Bu_2O (125 mL) and toluene (125 mL) was added dropwise within 45 min. Stirring was continued at 45 °C for 1 h, followed by cooling to 15 °C and dropwise addition of a solution of **6** (33.8 g, 0.1 mol) in toluene (380 mL) at 15 °C. The reaction mixture was stirred 3 h at this temperature, 2 M aqueous HCl (200 mL) was added and mixture was refluxed with stirring for 3 h. After cooling to room temperature, the organic layer was separated and the aqueous layer was extracted with toluene (4 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (4 × 55 mL), saturated aqueous NaCl (3 × 40 mL) and H_2O (4 × 45 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using EtOAc-petroleum ether (1:2) to afford the pure **7** as a colorless oil; yield: 24.6 g (70%); $[\alpha]_D^{22}$: −61.2 (*c* 1.0, $CHCl_3$) {Lit.[15] $[\alpha]_D^{20}$: −60 (*c* 0.9, $CHCl_3$)}; IR (nujol): ν = 2939, 1706, 1693, 1605, 1594, 1502, 1452, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.27 (dd, 1H, *J* = 12.9, 4.76 Hz), 2.64 (d, 1H, *J* = 12.9), 3.60 (s, 1H), 4.13 (dd, 1H, *J* = 7.8, 4.75 Hz), 4.17 (d, 1H, *J* = 15.4 Hz), 4.34 (d, 1H, *J* = 7.95 Hz), 4.36 (d, 1H, *J* = 15.4 Hz), 4.46 (d, 1H, *J* = 15.4 Hz), 4.67 (d, 1H, *J* = 15.4 Hz), 7.18–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 34.7, 46.4, 47.2, 59.3, 60.6, 62, 127.6, 127.7, 127.8, 128.65, 128.71, 136.8, 137, 159.8, 189.9; MS (EI): *m/z* (%) = 352 (M^+, 5), 323 (5), 277 (93), 264 (6), 91 (100), 65 (6).

(3a*S*,4*R*,6a*R*)-1,3-Dibenzyl-4-[(1*E*,3*E*)-4-methoxycarboxyl-1,3-butandienyl]-1*H*-tetrahydrothieno [3,4-*d*]imidazole-2(3*H*)-one (8)

A mixture of **7** (35.2 g, 0.1 mmol), diethyl 3-methoxycarbonyl-2-propenylidinephosphonate (23.6 g, 0.1 mmol), C-200 catalyst (9.66 g, 52 mmol) dioxane (120 mL), and H_2O (2.0 mL) was stirred at 70 °C for 2.5 h. After cooling to room temperature, 1.0 M aqueous HCl (75 mL) and CH_2Cl_2 (150 mL) were added. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 45 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 45 mL) and H_2O (3 × 45 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using EtOAc-petroleum ether (1:2) to afford the pure **8** as a colorless oil; yield: 39 g (90%); $[\alpha]_D^{22}$: +86 (*c* 1.0, CH_3OH) {Lit.[15] $[\alpha]_D^{22}$: +85.51 (*c* 1.16, CH_3OH)}; IR (nujol): ν=3020, 2920, 1700, 1650, 1600, 1510, 1450, 1370, 1260, 1150, 1020 cm^{-1}; ^1H NMR (C_6D_6): δ = 7.25 (m, 11H), 5.76 (d, 1H, *J* = 15.2 Hz), 5.53 (dd, 1H, *J* = 15.2, 10.78 Hz), 4.67 (t, 2H, *J* = 15.2 Hz), 3.42 (s, 3H), 3.27 (dd, 1H, *J* = 8.89, 3.86 Hz), 2.35 (dd, 1H, *J* = 12.25, 4.3 Hz), 2.22 (dd, 1H, *J* = 12.25, 5.8 Hz); ^{13}C NMR ($CDCl_3$): δ = 36.7, 37.0, 46.3, 46.7, 51.3, 55.1, 61.5, 65.9, 121.7, 127.5, 127.95, 128.5, 129.6, 136.7, 136.8, 138.6, 142.7, 158.9, 166.6; MS (EI): *m/z* (%) = 434 (M^+, 43), 402 (7), 277 (100), 264(13), 187 (15), 155 (9), 91 (76).

(3a*S*,4*S*,6a*R*)-1, 3-Dibenzyltetrahydro-1*H*-thieno[3,4-*d*]imidazole-2(3*H*)-one-4-ylpentanoic Acid (10)

1 M aqueous KOH (143 mL) and a catalytic amount of TBAB were added to a solution of **8** (13 g, 30 mmol) in CH_3OH (130 mL) at room temperature for 8 h. Then, the solvent was evaporated under reduced pressure to dryness. 1 M HCl (235 mL) and CH_2Cl_2 (200 mL) were added with stirring at 5–10 °C, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with saturated aqueous NaCl (3 × 45 mL) and H_2O (3 × 45 mL), and dried over Na_2SO_4. The solvent was evaporated. The residue was dissolved in EtOAc (125 mL) and hydrogenated under 10 atm of H_2 in the presence of $Pd(OH)_2$/C (1.1 g) at room temperature for 15 h. After the reduction was completed, the reaction mixture was filtered through a pad of celite, which was washed with EtOAc (3 × 10 mL). The filtrate was evaporated under reduced pressure to give the crude product, which was purified by recrystallization from *i*-PrOH/petroleum ether (bp 60–90 °C, 1:2) to afford the pure **10**; yield: 10.4 g (82%); mp 91–93 °C; $[\alpha]_D^{23}$: −26.6 (*c* 1.0, CH_3OH) {Lit.[18] mp 91–92 °C; $[\alpha]_D^{23}$: −26.8 (*c* 1.0, CH_3OH)}; IR (KBr): ν = 29.28, 1726, 1664, 1433, 1366, 1230, 1178, 951, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.59–1.64 (m, 6H), 2.33 (t, 2H, *J* = 6.55 Hz), 2.70 (4 × d, 2H, *J* = 2.35, 4.38 Hz), 3.08 (m,1H), 3.91 (dd, 1H, *J* = 5.55 Hz), 3.98 (m, 1H), 4.03, 4.15, 4.75, 5.00 (4 × d, 4H, *J* = 14.9, 15.1 Hz), 7.24–7.36 (m, 10H); MS (EI): *m/z* (%) = 423 (M^+, 37.3), 289 (18.3), 238 (10.8), 198 (2.4), 106 (49.3), 91 (100).

d-Biotin (1)

A stirred mixture of **10** (42.4 g, 0.1 mol) and 47% HBr (275 mL) was heated at reflux for 42 h. The cooled reaction mixture was extracted with toluene (3 × 60 mL) to remove the benzyl bromide and some impurities, and the toluene was then concentrated under reduced pressure to dryness. A solution of 3 M aqueous KOH (350 mL) and TBAB (1.5 g) were added to the residue and stirring was continued for 15 min at room temperature. A solution of diphosgene (59.4 g, 0.3 mol) in toluene (400 mL) was added dropwise over a period of 30 min, and the reaction mixture was stirred at room temperature for 6.5 h. The pH value of the reaction mixture was kept within the range 9–10 by addition of 3 M aqueous KOH. H_2O (200 mL) was added to the reaction mixture. The organic layer was separated, the aqueous layer was acidified to pH 2 with 2 M aqueous HCl with stirring to give a precipitate which was recrystallized from H_2O to afford the pure **1** as a white crystalline powder; yield: 20.1 g (82%); mp 231–233 °C, $[\alpha]_D^{22}$: +91.2 (*c* 1.0, 0.1 M NaOH) {Lit.[19] mp 232–233 °C; $[\alpha]_D^{22}$: +91.2 (*c* 1.0, 0.1 M NaOH)}; IR (KBr): ν = 3306–3243, 2704–2500, 1706, 1666 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.31–1.62 (m, 6H), 2.18 (t, 2H, *J* = 7.3 Hz), 2.58 (dd, 1H, *J* = 1.7 Hz), 2.81 (dd, 1H, *J* = 4.8, 12.5 Hz), 3.15 (m, 1H), 4.18 (m, 1H), 4.35 (m, 1H), 6.38 (s, 1H), 6.48 (s, 1H), 11.9 (br s, 1H); MS (EI): *m/z* (%) = 245 ($M^+ + 1$, 15), 227 (9), 184 (25), 112 (26), 97 (100), 85 (66).

X-Ray Structure Analysis of Compound 4

Crystals of $C_{20}H_{20}N_2O_5$ (Mw: 368.38) suitable for X-ray analysis were obtained from EtOAc/cyclohexane (1:1). A colorless

monoclinic crystal of dimensions $0.25 \times 0.15 \times 0.10$ mm was mounted on a Rigaku AFC7R diffractometer. Determination of the cell parameters was performed by least-squares refinement of 25 reflections. The compound crystallized in the monoclinic system, space group $P2_1$ with $a = 5.750$ (2), $b = 9.302$ (2), $c = 17.014$ (4) Å, $\beta = 93.92$ (3)°, $v = 907.9$ (4) Å^3, $T = 295$ (2) K, $Z = 2$, μ(Mo-Kα) $= 0.098$ mm^{-1}, $D_{calcd.} = 1.348$ g cm^{-3}, F(000) = 388 reflections were collected in the range of $1.20 < \theta < 25.17°$ using Mo-Kα radiation (graphite monochromator, $\lambda = 0.71073$ Å), ω-2 scan mode. The structure was solved by direct methods and expanded using difference Fourier techniques and refined by full-matrix least-square to $R = 0.0520$, $R\omega = 0.1210$ with $\omega = 1/[\sigma^2 (Fo + (0.1035P^2 + 1.3711P))R$ [where $P = (Fo^2 + 2Fc^2)/3$] by using the 1729 observed reflections having $I > 2.00\sigma(I)$ for 247 parameters refined. All non-hydrogen atoms were refined anisotropically.

The crystallographic data has been deposited in Cambridge Crystallographic Data Centre with depository number 249374.Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

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