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Total synthesis of (+)-biotin via a quinine-mediated asymmetric alcoholysis of *meso*-cyclic anhydride strategy

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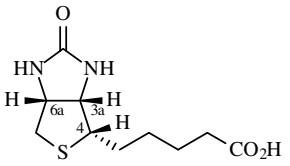
ABSTRACT

A concise asymmetric total synthesis of (+)-biotin **1** has been accomplished in which the absolute stereochemistry of C_{3a}, C_{6a} of **1** was established by utilizing an efficient and practical quinine-mediated asymmetric alcoholysis of *meso*-cyclic anhydride **2** in a single step, the C_4 stereochemistry was installed by a direct stereoselective ionic hydrogenation of the thiolactol **7**.

1. Introduction

(+)-Biotin **1** is one of the water-soluble B-complex vitamins bearing a *cis*-fused bi-heterocyclic core and three adjacent stereogenic centers in the *all-cis* configuration (Fig. 1). Due to its unique structure and biological importance for human nutrition and animal health,[1] this vitamin has attracted considerable attention from both industry and academia for more than 50 years.[2] In the previously reported approaches toward **1**, the stereochemistry of C_{3a}, C_{6a} of **1** was established by different strategies, such as diastereomeric or enzymatic resolution,[3] chiral pool methods,[4] and asymmetric syntheses,[5] while the C_4 stereocenter was installed in most cases via a catalytic hydrogenation under high temperature and high hydrogen pressure.[2] In continuation of our work on the total synthesis of (+)-biotin,[6] we herein report a concise total synthesis of **1**, featuring a highly efficient asymmetric alcoholysis and a mild ionic hydrogenation as the key steps to incorporate the three contiguous stereogenic centers.



(+)-Biotin **1**

Figure 1. The structure of (+)-biotin.

The recently emerged catalytic asymmetric alcoholysis[7] of *meso*-cyclic anhydrides has provided a powerful protocol for the synthesis of a broad range of important chiral building blocks, such as hemiesters, α-amino acids, and α-hydroxy acids. The cinchona alkaloids were found to be excellent directing additives, which could promote the ring opening of a wide variety of *meso*-cyclic anhydrides to afford the corresponding hemiester with high enantioselectivity in excellent yield.[8] Herein, we report an inexpensive and easily available cinchona alkaloid-quinine-mediated desymmetrization of *meso*-cyclic anhydride **2** to prepare (4*S*,5*R*)-hemiester **3**, a direct precursor to (3a*S*,6a*R*)-lactone **4**, to complete an efficient total synthesis of **1**.

2. Results and discussion

Our project started with the screening of the optimal reaction conditions by using methanol as the test nucleophile in the quinine-mediated asymmetric alcoholysis of commercially available cyclic anhydride **2** to prepare the key chiral building block-(3a*S*,6a*R*)-lactone **4** (Scheme 1). The results are illustrated in Table 1. As shown in Table 1, the desired hemiester **3a** was obtained in nearly quantitative yield and good enantioselectivity (78.1% ee) when the asymmetric alcoholysis of **2** was run at −50 °C in a mixed solvent of toluene/carbon tetrachloride (1:1) (entry 1). Increasing the reaction temperature dramatically decreased the enantiomeric excess of **3a** and reached a minimum at around 25 °C (entries 2–5). A major effect was noted upon varying the concentration of the substrate **2**. An increase in ee occurred upon lowering the substrate concentration (entries 1, 6, and 7), allowing the formation of hemiester **3a** in 82% ee (entry 7) at a lower reaction concentration (0.02 M). Also, a number of solvents were screened in the asymmetric alcoholysis including toluene, toluene/carbon tetrachloride (1:1), diethyl ether, tetrahydrofuran, ethyl acetate, and acetone

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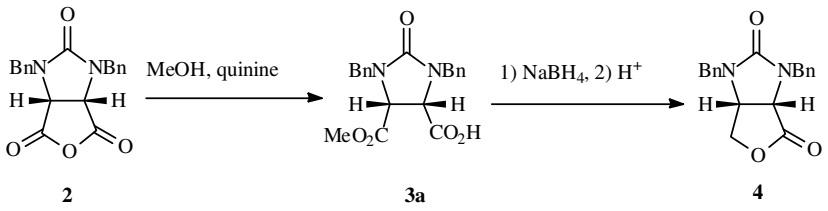
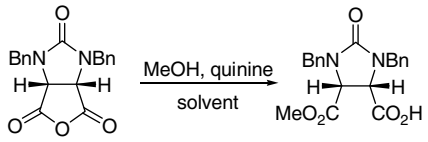


Scheme 1. The preparation of (3a*S*,6a*R*)-lactone **4**.

Table 1
Optimization of the reaction conditions in the asymmetric alcoholysis of cyclic anhydride **2**[a]

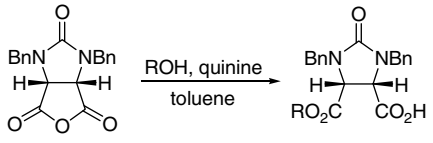


2 **3a**

Entry	Temperature (°C)	Solvent	Concentration of **2** (M)	Yield[b] (%)	ee[c] (%)
1	−50	CCl_4/toluene (1:1)	0.05	99	78.1
2	−40	CCl_4/toluene (1:1)	0.05	97	76
3	−20	CCl_4/toluene (1:1)	0.05	95	73
4	0	CCl_4/toluene (1:1)	0.05	92	64
5	25	CCl_4/toluene (1:1)	0.05	90	58
6	−50	CCl_4/toluene (1:1)	0.1	98	72
7	−50	CCl_4/toluene (1:1)	0.02	99	82
8	−50	Et_2O	0.05	–[d]	–
9	−50	Toluene	0.05	99	77
10	−50	THF	0.05	90	62
11	−50	AcOEt	0.05	93	53
12	−50	Acetone	0.05	80	40

[a] Reaction conditions: **2** (3.36 g, 10 mmol), MeOH (1.22 mL, 30 mmol), quinine (3.57 g, 11 mmol), 72 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis of the corresponding lactones, which were obtained by selective reduction of the ester group with $LiBEt_3H$ followed by acid-catalyzed lactonization.[9]
[d] Conversion <10% after 96 h.

Table 2
Asymmetric alcoholysis of cyclic anhydride **2** with different alcohols[a]



2 **3**

Entry	ROH	Yield[b] (%)	ee[c] (%)
1	Methanol (**a**)	99	82
2	Ethanol (**b**)	98	84
3	1-Propanol (**c**)	90	80
4	Trifluoroethanol (**d**)	90	41
5	2-Propanol (**e**)	–[d]	–
6	Allyl alcohol (**f**)	94	80
7	Propargyl alcohol (**g**)	95	86
8	Benzyl alcohol (**h**)	93	78
9	Cyclohexanol (**i**)	–[d]	–
10	*trans*-Cinnamyl alcohol (**j**)	91	77

[a] Reaction conditions: **2** (3.36 g, 10 mmol), ROH (30 mmol), quinine (3.57 g, 11 mmol), in toluene (500 mL), at −50 °C, 72 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis of the corresponding lactones, which were obtained by selective reduction of the ester group with $LiBEt_3H$ followed by acid-catalyzed lactonization.[9]
[d] Conversion <10% after 96 h.

and it was found that non-polar toluene was most suitable for this reaction in which 77% ee of **3a** was obtained (entry 9). Furthermore, no reaction was observed when the asymmetric alcoholysis was performed in diethyl ether (entry 8).

Next, we examined the asymmetric alcoholysis of **2** with different alcohols as nucleophile under the above-optimized reaction conditions. As Table 2 shows, in terms of enantioselectivity, propargyl alcohol turned out to be the best (86% ee, entry 7) and trifluoroethanol proved to be the worst (41% ee, entry 4), while 2-propanol and cyclohexanol were inert to the reaction (entries 5 and 9). No significant difference was observed among the remaining alcohols. The enantiomeric excess of the crude hemiesters (**3a**–**c**, **3f**–**h**) could be increased to 90–97% by a single recrystallization from ethyl acetate/cyclohexane (1:1). In the event, **3g** crystallized nicely from ethyl acetate/cyclohexane (1:1), allowing the ee to be enriched to 97% in 83% yield. The relative configuration of the hemiesters was confirmed by an X-ray crystallographic analysis of the representative compound **3g**, as depicted in Figure 2 while the absolute configuration of **3g** was determined as (4*S*) and (5*R*) by comparison of the specific rotation of the lactone **4**, transformed from **3g**, with the reported values.[6h]

It is worth noting that the alkaloid used in the asymmetric alcoholysis can be recovered quantitatively by a simple acidic extraction followed by basification of the aqueous phase, extraction of the alkaline aqueous solution with CH_2Cl_2, and evaporation of the solvent. To demonstrate the reusability of quinine, we performed a preparative scale reaction by using the recovered quinine as a directing additive and methanol as a nucleophile. The desired hemiester **3a** was obtained with 82% ee in 99% yield.

With this efficient method in hand for the preparation of the (4*S*,5*R*)-hemiester, the next task was to convert the chiral hemiester into (3a*S*,6a*R*)-lactone **4** via a one-pot reduction and lactonization (Scheme 2). Thus, chemoselective reduction of the ester group of **3g** with $NaBH_4$ in the presence of $CaCl_2$ in anhydrous ethanol, followed by acid-catalyzed lactonization afforded the important intermediate (3a*S*,6a*R*)-lactone **4** in 90% yield with 97% ee. Treatment of **4** with sodium thioacetate in DMF at 150 °C provided the key building block-(3a*S*,6a*R*)-thiolactone **5** in 72% isolated yield.

We then proceeded to install the carboxybutyl side chain at the C_4 of thiolactone **5** using a modified Fukuyama coupling procedure.[10] Treatment of **5** with the in situ generated zinc reagent **6** in the presence of the nanopalladium (LDH–Pd^0) catalyst[11] allowed a convenient installation of the carboxybutyl side chain to afford thiolactol **7** as an inseparable mixture of diastereoisomers (ratio 3:1, as determined by ^1H NMR spectroscopy) (Scheme 3). The next

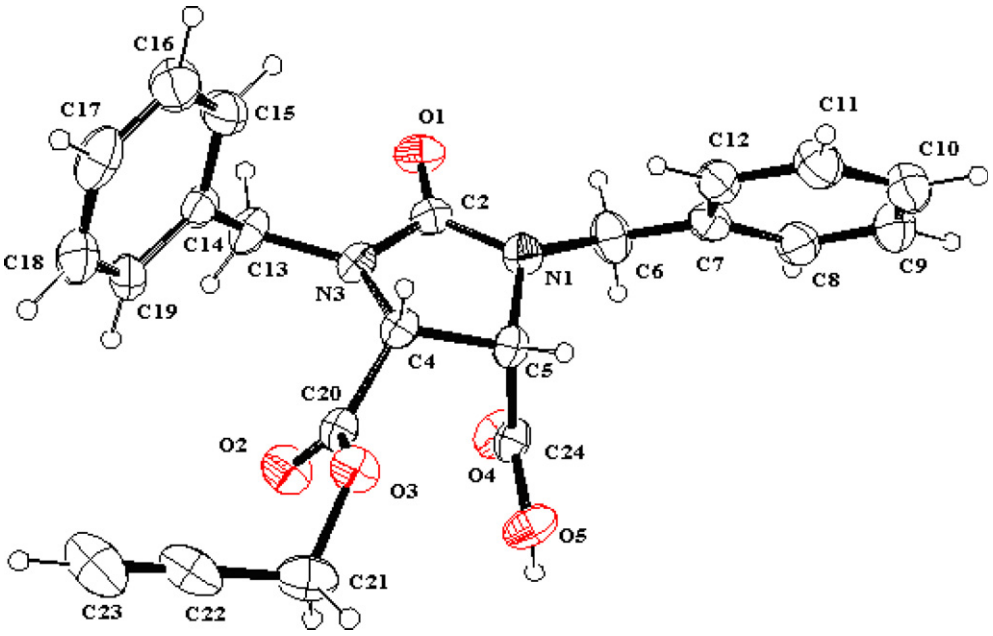
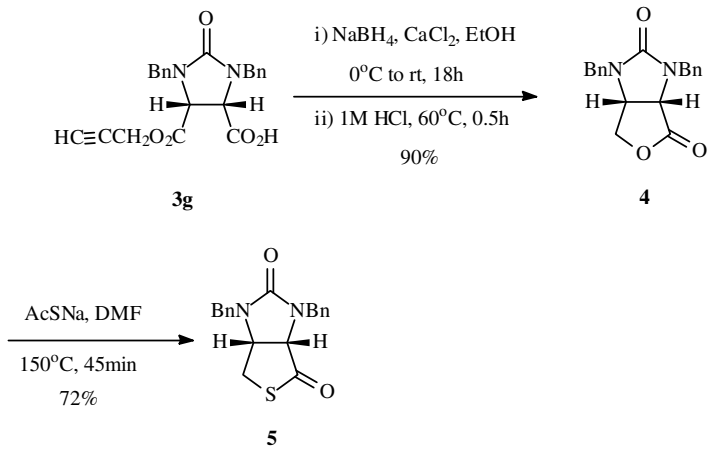


Figure 2. ORTEP drawing of the X-ray structure of hemiester **3g**.



Scheme 2. Synthesis of (3a*S*,6a*R*)-thiolactone **5**.

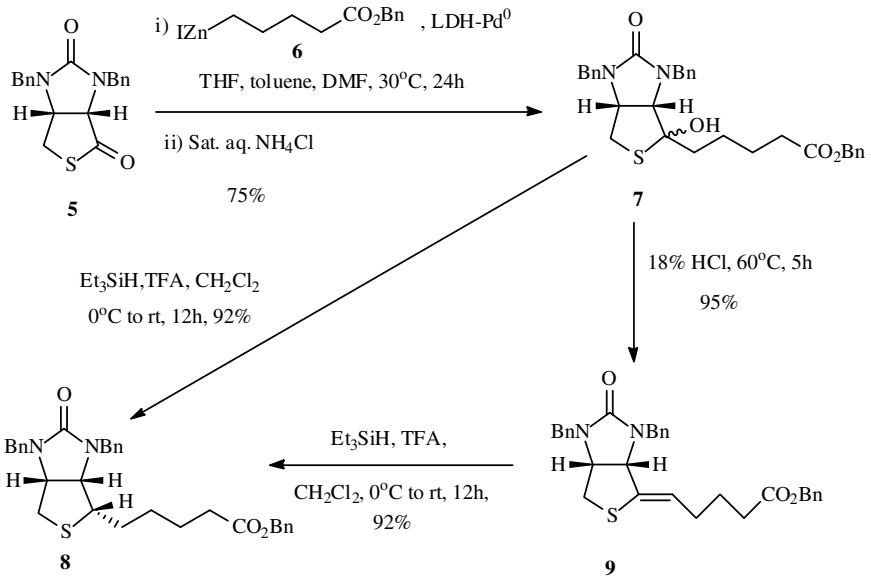
step was to eliminate the hydroxyl group of thiolactol **7** to incorporate the required C_{4S} stereocenter. In previously reported approaches toward **1**, the thiolactol intermediate was usually subjected directly to an acid treatment without purification to afford an olefin derivative, catalytic hydrogenation under high temperature and pressure created the third stereogenic center. To avoid the violent reaction conditions and catalytic poison encountered in the catalytic hydrogenation, we attempted to reduce the tertiary hydroxyl group of **7** directly, via an ionic hydrogenation.[12] Fortunately, treatment of **7** with Et_3SiH in the presence of TFA at ambient temperature led to the pentanoate **8** as a single diastereoisomer[13] with the required C_{4S} configuration. The stereochemistry of C_4 was confirmed by ^1H–^1H NOESY NMR spectral analysis (Fig. 3).[14] Alternatively, the pentanoate **8** could also be obtained by the same hydride reduction of compound **9**, the dehydration product of **7**.

A plausible mechanism of this hydride reduction is proposed as shown in Figure 4. The ionic hydrogenation proceeds through the formation of a carbenium intermediate, then hydride attack from the *re*-face to yield the kinetic-favored **8** as the major product, while the formation of **10** by *si*-face attack is nearly neglectable.

Finally, on refluxing **8** with 47% aq HBr, a one-pot debenzylation, hydrolysis, and ring opening reaction furnished the diamine·2HBr salt which, without purification, was allowed to react with triphosgene at ambient temperature in the presence of activated charcoal as catalyst[15] to afford (+)-biotin in 82% yield (Scheme 4), which was identical in all respects to that previously described in the literature.[6h]

3. Conclusions

In conclusion, a facile, concise, and efficient catalytic asymmetric total synthesis of (+)-biotin has been accomplished from the easily accessible cyclic anhydride **2** in 28% overall yield. The pivotal reaction sequence includes a quinine-mediated asymmetric desymmetrization and a mild ionic hydrogenation for the installation of the



Scheme 3. Introduction of carboxybutyl side chain.

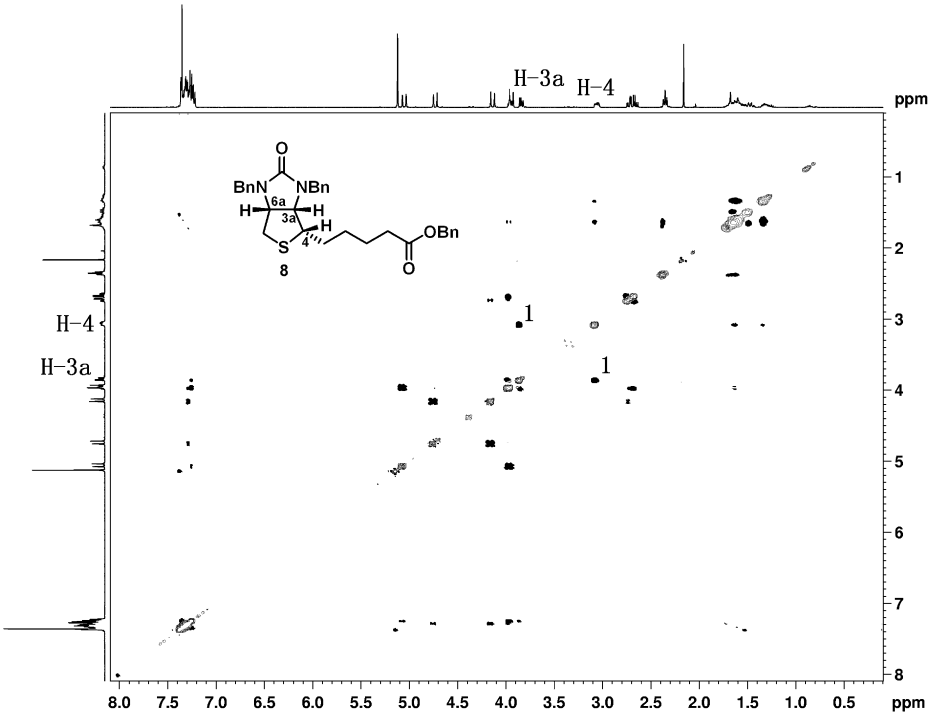


Figure 3. 2D NOESY spectrum of **8**. *Note*: peak **1** in the figure is the cross peak between H-3a (δ 3.84 ppm) and H-4 (δ 3.03–3.06 ppm).

three contiguous stereocenters. We believe the efficient synthetic method should permit ready access to this important vitamin.

4. Experimental

4.1. General

THF was distilled from sodium/benzophenone, dichloromethane and toluene from calcium hydride, and DMF from calcium hydride under reduced pressure. The alcohols used were purified according to standard methods.[16] Other reagents were obtained from commercial sources and used as received. Unless otherwise noted, all reactions were carried out under argon or nitrogen using standard Schlenk and vacuum line techniques. All melting points are uncorrected, and were measured on a *WRS-1B* digital melting-point apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) or DMSO (^{1}H δ 2.49) and $CDCl_3$ (^{13}C δ 77.0) or DMSO-d_6 (^{13}C δ 39.5) as internal standards. *J*-values are given in Hertz. Mass spectra were recorded on a Waters Quattro Micromass instrument using electrospray ionization (ESI) techniques. IR spectra were recorded on a Jasco FT/IR-4200 spectrometer. Optical rotations were obtained on a Jasco P1020 digital polarimeter. HPLC analysis was performed using a

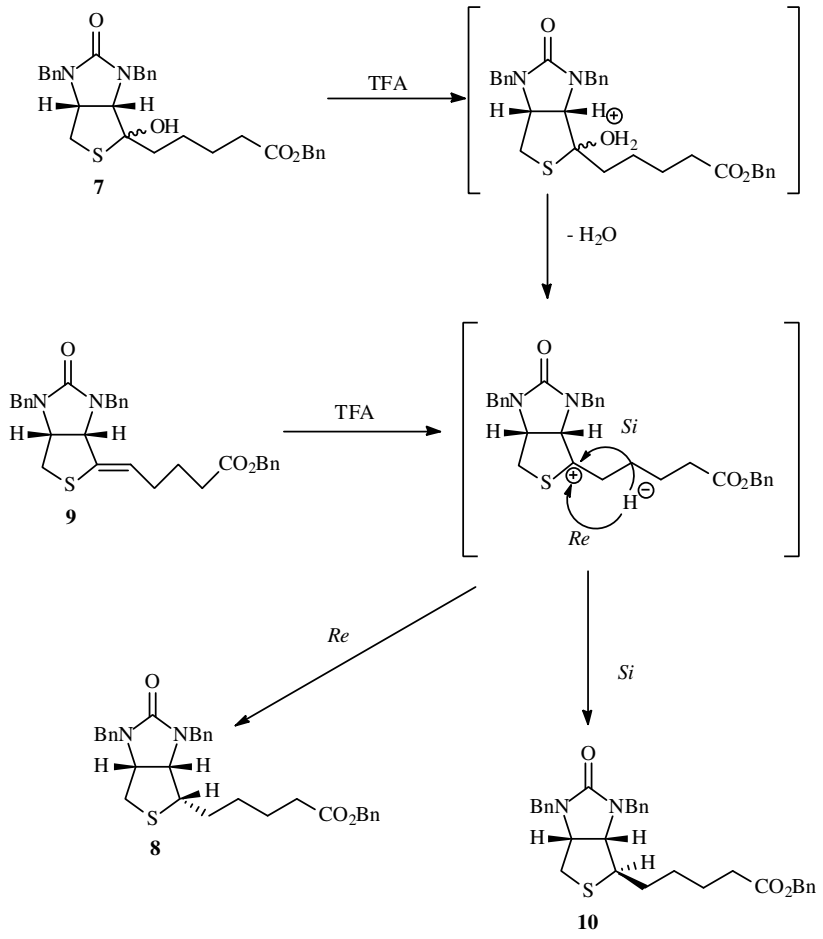
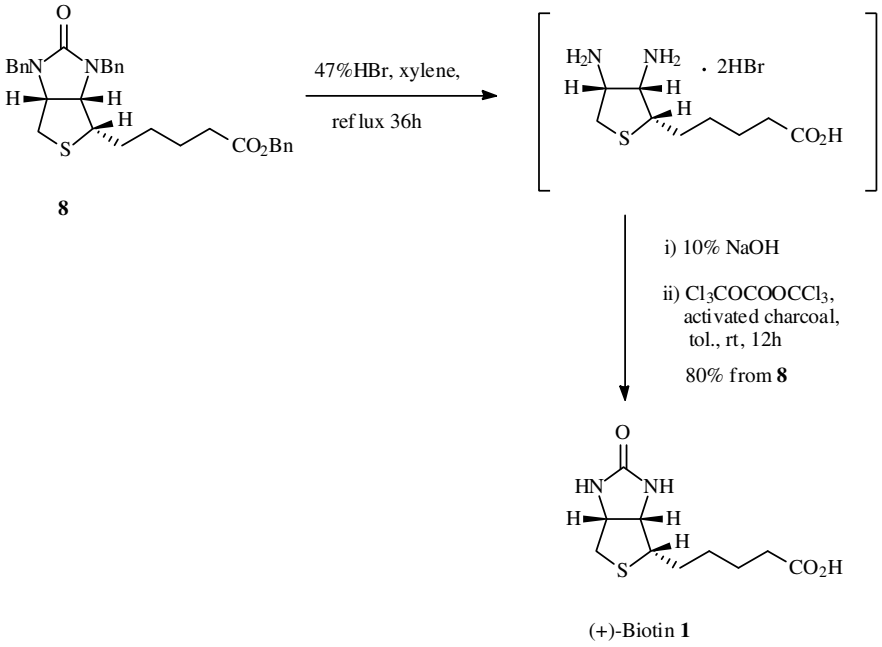


Figure 4. Proposed mechanism for the ionic hydrogenation.



Scheme 4. Synthesis of (+)-biotin.

Chiralcel AD-H column, 4.6 × 250 mm, λ = 210 nm. Elemental analyses were performed on a CARLOERBA 1106 instrument and the results of elemental analyses for C, H, N, and S were within ±0.4% of the theoretical values.

4.2. General procedure for the asymmetric alcoholysis of cyclic anhydride 2

To a solution of quinine (3.57 g, 11 mmol) in toluene (500 mL) was added **2** (3.36 g, 10 mmol) at −50 °C under nitrogen. After being stirred for 10 min, alcohol (30 mmol) was added dropwise and then the resulting mixture was stirred at the same temperature for 72 h. During this period, the material gradually turned clear. Subsequently, the resulting solution was concentrated in vacuo to dryness, the residue was dissolved in ethyl acetate. The solution was washed with 2 M HCl and brine. After phase separation, the organic phase was dried over Na_2SO_4, and concentrated to afford the desired product with (**3h**, **3j**) or without (**3a**–**c**, **3f**, and **3g**) further purification by flash chromatography.

To recover quinine, the acidic aqueous phase was basified with Na_2CO_3 and extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to recover quinine (pure as determined by ^{1}H NMR) quantitatively.

4.2.1. (4*S*,5*R*)-1,3-Dibenzyl-5-(methoxycarbonyl)-2-oxo-imidazolidine-4-carboxylic acid 3a

Compound (4*S*,5*R*)-**3a** was prepared by the quinine-mediated ring opening of **2** in the presence of methanol in 99% yield. Mp: 144–146 °C; $[\alpha]_D^{25} = +2.2$ (*c* 1.0, $CHCl_3$); [Lit.[6h] Mp: 150–151 °C, $[\alpha]_D^{25} = +7.31$ (*c* 1.0, DMF)]; ee = 82%; IR (KBr): 3258, 2943, 1756, 1713, 1449, 1411, 1252, 968, 799, 598, 458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 10H), 6.85 (br s, 1H), 5.09 (d, *J* = 14.8 Hz, 1H), 4.98 (d, *J* =14.8 Hz, 1H), 4.13–4.04 (m, 4H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 168.5, 159.5, 135.57, 135.52, 128.85, 128.79, 128.64, 128.56, 127.98, 127.93, 57.3, 56.7, 52.6, 46.89, and 46.80; ESI-MS *m*/*z* 391.1 $[M+Na]^+$.

4.2.2. (4*S*,5*R*)-1,3-Dibenzyl-5-(ethoxycarbonyl)-2-oxo-imidazolidine-4-carboxylic acid 3b[17]

Compound (4*S*,5*R*)-**3b** was prepared by the quinine-mediated ring opening of **2** in the presence of ethanol in 98% yield. Mp: 130–132 °C; $[\alpha]_D^{25} = +3.7$ (*c* 1.0, $CHCl_3$); ee = 84%; IR (KBr): 3059, 2982, 1746, 1657, 1469, 1363, 1209, 1026, 747, 701, 597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.32–7.20 (m, 10H), 5.09 (d, *J* = 14.8 Hz, 1H), 4.99 (d, *J* = 14.8 Hz, 1H), 4.12–4.04 (m, 6H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 167.9, 159.6, 135.62, 135.57, 128.83, 128.77, 128.61, 128.56, 127.94, 127.90, 62.0, 57.2, 56.7, 46.8, 46.7, and 13.9; ESI-MS *m*/*z* 405.3 $[M+Na]^+$.

4.2.3. (4*S*,5*R*)-1,3-Dibenzyl-5-(*n*-propoxycarbonyl)-2-oxo-imidazolidine-4-carboxylic acid 3c[17]

Compound (4*S*,5*R*)-**3c** was prepared by the quinine-mediated ring opening of **2** in the presence of *n*-propanol in 90% yield. Mp: 78–82 °C; $[\alpha]_D^{25} = +2.5$ (*c* 1.0, $CHCl_3$); ee = 80%; IR (KBr): 3065, 2984, 1744, 1655, 1469, 1359, 1209, 1073, 952, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.75 (br s, 1H), 7.31–7.20 (m, 10H), 5.08 (d, *J* = 14.8 Hz, 1H), 5.01 (d, *J* = 14.8 Hz, 1H), 4.10–3.92 (m, 6H), 1.58 (tq, *J* = 7.2, 7.2 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 168.1, 159.7, 135.61, 135.59, 128.84, 128.80, 128.63, 128.59, 127.95, 127.94, 67.6, 57.3, 56.8, 46.8, 46.7, 21.6, and 10.3; ESI-MS *m*/*z* 397.2 $[M+H]^+$, 419.2 $[M+Na]^+$.

4.2.4. (4*S*,5*R*)-1,3-Dibenzyl-5-(trifluoroethoxycarbonyl)-2-oxo-imidazolidine-4-carboxylic acid 3d[18]

Compound (4*S*,5*R*)-**3d** was prepared by the quinine-mediated ring opening of **2** in the presence of trifluoroethanol in 90% yield. Mp: 234.8–236.4 °C; $[\alpha]_D^{25} = +3.2$ (*c* 1.0, $CHCl_3$); ee = 41%; IR (KBr): 3443, 2984, 1756, 1664, 1468, 1284, 1206, 1187, 750, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.19 (m, 10H), 5.10 (d, *J* = 14.8 Hz, 1H), 5.00 (d, *J* = 14.8 Hz, 1H), 4.75 (br s, 1H), 4.46–4.27 (m, 2H), 4.18–4.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 166.7, 159.4, 135.3, 135.1, 128.9, 128.63, 128.59, 128.17, 128.09, 61.2, 60.8, 56.9, 56.4, 46.9, and 46.7; ESI-MS *m*/*z* 415.1 $[M+H]^+$, 437.1 $[M+Na]^+$.

4.2.5. (4*S*,5*R*)-1,3-Dibenzyl-5-(allyloxycarbonyl)-2-oxo-imidazolidine-4-carboxylic acid 3f

Compound (4*S*,5*R*)-**3f** was prepared by the quinine-mediated ring opening of **2** in the presence of allyl alcohol in 94% yield. Mp: 107.7–109.8 °C; $[\alpha]_D^{25} = +7.81$ (*c* 1.0, $CHCl_3$); ee = 80%; IR (KBr): 3061, 2929, 1755, 1657, 1450, 1356, 1235, 1200, 936, 754, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.30–7.18 (m, 10H), 5.84–5.74 (m, 1H), 5.26–5.18 (m, 2H), 5.06 (d, *J* = 14.8 Hz, 1H), 4.98 (d, *J* = 14.8 Hz, 1H), 4.54–4.43 (m, 2H), 4.12–4.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.7, 159.7, 135.47, 135.43, 130.9, 128.73, 128.54, 128.50, 127.86, 119.4, 66.4, 57.2, 56.7, 46.7, and 46.6; ESI-MS *m*/*z* 395.3 $[M+H]^+$, 417.3 $[M+Na]^+$. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.87; H, 5.75; N, 7.22.

4.2.6. (4*S*,5*R*)-1,3-Dibenzyl-5-(propargyloxycarbonyl)-2-oxo-imidazolidine-4-carboxylic acid 3g

Compound (4*S*,5*R*)-**3g** was prepared by quinine-mediated ring opening of **2** in the presence of propargyl alcohol in 95% yield. Mp: 132.7–135.8 °C; $[\alpha]_D^{25} = +14.3$ (*c* 1.0, $CHCl_3$); ee = 86%; IR (KBr): 3299, 3026, 2919, 1751, 1652, 1464, 1440, 1203, 978, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 10H), 6.62 (br s, 1H), 5.08 (d, *J* = 14.8 Hz, 1H), 5.00 (d, *J* = 14.8 Hz, 1H), 4.66–4.56 (m, 2H), 4.12–4.06 (m, 4H), 2.50 (t, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 167.3, 159.5, 135.48, 135.36, 128.87, 128.84, 128.67, 128.60, 128.02, 128.00, 76.43, 75.97, 57.04, 56.51, 53.1, 46.85, 46.78; ESI-MS *m*/*z* 393.3 $[M+H]^+$, 415.3 $[M+Na]^+$. After recrystallization from ethyl acetate/cyclohexane (1:1), the enantiomerically pure (4*S*,5*R*)-**3g** was obtained in 83% yield, Mp: 135.8–137.8 °C; $[\alpha]_D^{25} = +15.6$ (*c* 1.0, $CHCl_3$); ee = 97%. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.13; N, 7.14. Found: C, 67.52; H, 5.10; N, 7.25.

4.2.7. (4*S*,5*R*)-1,3-Dibenzyl-5-(benzyloxycarbonyl)-2-oxo-imidazolidine-4-carboxylic acid 3h[19]

Compound (4*S*,5*R*)-**3h** was prepared by the quinine-mediated ring opening of **2** in the presence of benzyl alcohol, and purified by flash chromatography (AcOEt/hexane 2:1) in 93% yield as a viscous oil, which slowly crystallized upon standing. Mp: 57.7–60.6 °C; $[\alpha]_D^{25} = +12.2$ (*c* 1.0, $CHCl_3$); ee = 78%; IR (KBr): 3031, 2945, 1752, 1664, 1454, 1236, 1201, 967, 741, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.10 (m, 15H), 5.12–4.97 (m, 4H), 4.11–4.00 (m, 4H), 3.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.8, 159.5, 135.65, 135.53, 128.83, 128.76, 128.70, 128.63, 128.61, 128.58, 127.94, 127.89, 67.7, 57.2, 56.5, 46.80, 46.79; ESI-MS *m*/*z* 467.2 $[M+Na]^+$.

4.2.8. (4*S*,5*R*)-1,3-Dibenzyl-5-[(2*E*)-3-phenyl-2-propenyl-oxycarbonyl]-2-oxo-imidazolidine-4-carboxylic acid 3j

Compound (4*S*,5*R*)-**3j** was prepared by the quinine-mediated ring opening of **2** in the presence of *trans*-cinnamyl alcohol, and purified by flash chromatography (AcOEt/hexane 2:1) in 91% yield as a viscous oil. $[\alpha]_D^{25} = +22.9$ (*c* 1.0, $CHCl_3$); ee = 77%; IR (KBr): 3028, 2941, 1752, 1665, 1450, 1239, 1198, 966, 747, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (br s, 1H), 7.42–7.27 (m, 15H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.24 (dt, *J* = 16.0, 6.4 Hz, 1H), 5.18 (d, *J* = 15.2 Hz, 1H), 5.09 (d, *J* = 15.2 Hz, 1H), 4.81–4.67 (m, 2H), 4.27–4.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.4, 159.7, 135.56, 135.13, 135.05, 134.47, 128.38, 128.19, 127.78, 127.52,

126.30, 121.59, 65.9, 60.2, 57.1, 56.6, 46.4, 46.3; ESI-MS *m*/*z* 493.4 $[M+Na]^+$, 509.4 $[M+K]^+$. Anal. Calcd for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.95. Found: C, 71.17; H, 5.33; N, 5.76.

4.3. (3a*S*,6a*R*)-1,3-Dibenzyl-tetrahydro-4*H*-furo[3,4-*d*]-imidazole-2,4(1*H*)-dione 4

To a solution of **3g** (3.92 g, 10 mmol) and granulated $CaCl_2$ (1.11 g, 10 mmol) in anhydrous ethanol (40 mL) was added $NaBH_4$ (1.14 g, 30 mmol) in three parts at 0 °C. The resulting mixture was allowed to stir for 1 h at 0 °C followed by another 18 h at 25 °C. Then 5% aq HCl (30 mL) was added and the resultant solution was stirred for 0.5 h at 55–60 °C. To the solution, H_2O (50 mL) was added and then cooled with an ice bath. Colorless crystals precipitated and were filtered, and dried to afford **4**, which was pure enough for use (2.9 g, 90%). Mp:119.2–120.5 °C; $[\alpha]_D^{25} = +60.5$ (*c* 2.0, $CHCl_3$) [Lit.[6h] Mp: 119–121 °C; $[\alpha]_D^{25} = +61.3$ (*c* 2.0, $CHCl_3$)]; ee = 97%; IR (KBr): 3031, 2919, 1775, 1706, 1415, 1365, 1237, 1209, 1146, 970, 754, 700, 639, 527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.36 (m, 10H), 5.05 (d, *J* = 15.2 Hz, 1H), 4.63 (d, *J* = 15.2 Hz, 1H), 4.37 (dd, *J* = 10.4 Hz, 15.2 Hz, 2H), 4.09–4.16 (m, 3H), 3.92 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 158.1, 136.0, 135.9, 129.0, 128.8, 128.7, 128.2, 128.0, 127.8, 70.1, 54.3, 52.4, 46.9, and 45.2; ESI-MS *m*/*z* 345.2 $[M+Na]^+$.

4.4. (3a*S*,6a*R*)-1,3-Dibenzyl-tetrahydro-4*H*-thieno[3,4-*d*]-imidazole-2,4(1*H*)-dione 5

To a solution of **4** (5 g, 15.5 mmol) in DMF (5 mL) was added AcSNa (1.8 g, 18.3 mmol) at 140 °C under the protection of argon. The mixture was stirred at 150 °C for 45 min, then cooled to rt. Thirty millilitres of CH_2Cl_2 and 30 mL of water was added, after which the aq phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from *iso*-propanol to afford **5** as a white solid, 3.75 g, 72%. Mp: 124–126 °C; $[\alpha]_D^{25} = +90.5$ (*c* 1.0, $CHCl_3$) [Lit.[6h] Mp: 125–126 °C; $[\alpha]_D^{25} = +90.2$ (*c* 1.0, $CHCl_3$)]; IR (KBr): 3030, 2934, 2889, 1703, 1697, 1453, 1412, 1361, 1218, 1148, 1051, 997, 903, 808, 66698, 647, 581, 485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 10H), 5.03 (d, *J* = 14.8 Hz, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.36 (d, *J* = 14.8 Hz, 1H), 4.15–4.11 (m, 1H), 3.81 (d, *J* = 8.0 Hz, 1H), 3.37 (dd, *J* = 12.4, 5.6 Hz, 1H), 3.28 (dd, *J* = 12.4, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 158.2, 136.4, 136.2, 128.87, 128.78, 128.66, 128.0, 127.91, 127.73, 62.1, 55.8, 46.5, 45.2, and 33.0; ESI-MS *m*/*z* 361.1 $[M+Na]^+$.

4.5. Benzyl(3a*S*,4*RS*,6a*R*)-5-(1,3-dibenzyl-2,3,3a,4,6,6a-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-5-hydroxyl)pentanoate 7

To a suspension of zinc dust (0.528 g, 8.07 mmol) in THF (2.0 mL) and toluene (1.5 mL) was added bromine (0.33 g, 2.06 mmol) dropwise at 10–20 °C, after which the mixture was heated to 50 °C. Benzyl 5-iodopentanoate (1.31 g, 4.13 mmol) was then added dropwise to the mixture at 50–60 °C. After being stirred at the same temperature for 1 h, the zinc reagent **6** was formed, then the mixture was cooled to 30 °C. A solution of compound **5** (1.0 g, 2.95 mmol) in THF (2 mL), toluene (5 mL), DMF (0.5 mL), and LDH–Pd^0 (0.16 g, 0.15 mmol) were added in one part and the resulting mixture was stirred at 30 °C for 24 h. Saturated aq NH_4Cl (15 mL) was added, the mixture was stirred at rt for 0.5 h, and then filtered. The filtrate was extracted with AcOEt. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/hexane 1:2) to give **7** as an inseparable diastereoisomeric mixture (1.17 g, 75%; 3:1 by ^1H NMR). Viscous oil. IR (neat): 3340, 2938, 1730, 1684, 1451, 1240, 1158, 963, 738, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.13 (m, 15H), 5.13 (d, *J* = 15.2 Hz, 0.6H), 5.10 (s, 0.5H), 5.07 (s, 1.5H), 5.07 (d, *J* = 15.6 Hz, 0.3H), 4.86 (d, *J* = 15.2 Hz, 0.6H), 4.81 (d, *J* = 15.2 Hz, 0.2H), 4.36 (s, 0.6H), 4.12–3.89 (m, 3.0H), 3.68 (d, *J* = 8.4 Hz, 0.2H), 3.60 (d, *J* = 10.0 Hz, 0.6H), 3.33 (s, 0.2H), 2.99–2.95 (m, 0.8H), 2.81–2.77 (m, 0.8H), 2.33–2.25 (m, 2.5H), 2.01 (s, 0.7H), 1.90–1.85 (m, 0.7H), 1.67–1.36 (m, 4.5H), 1.25–1.21 (t, *J* = 6.8 Hz, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.11, 173.05, 161.16, 160.22, 136.85, 136.55, 136.36, 135.88, 128.66, 128.60, 128.55, 128.48, 128.45, 128.39, 128.35, 128.07, 128.03, 127.99, 127.90, 127.86, 127.73, 127.57, 127.52, 127.38, 127.35, 98.9, 95.5, 68.8, 66.0, 65.9, 61.3, 60.5, 60.1, 48.6, 47.1, 46.0, 45.8, 41.2, 36.8, 34.1, 33.89, 33.85, 33.71, 33.65, 25.36, 25.14, 24.96, 24.80, 23.95, 20.83, and 14.0; ESI-MS *m*/*z* 553.4 $[M+Na]^+$. Anal. Calcd for $C_{31}H_{34}N_2O_4S$: C, 70.16; H, 6.46; N, 5.28; S, 6.04. Found: C, 70.33; H, 6.32; N, 5.36; S, 6.25.

4.6. Benzyl(3a*S*,4*S*,6a*R*)-5-(1,3-dibenzyl-2,3,3a,4,6,6a-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-5-yl)pentanoate 8

To a solution of **7** (5 g, 9.4 mmol), triethylsilane (3.29 g, 28.3 mmol) in CH_2Cl_2 (50 mL) was added trifluoroacetic acid (6.45 g, 56.6 mmol) dropwise at 0 °C. After the completion of addition, the mixture was allowed to rise to rt and stirred for 12 h. The reaction was quenched with saturated aq $NaHCO_3$ and then extracted with AcOEt, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/hexane 1:2) to give **8** as a viscous oil (4.45 g, 92%). $[\alpha]_D^{25} = -20.7$ (*c* 1.0, MeOH); IR (neat): 3030, 2930, 1731, 1698, 1449, 1237, 1160, 968, 745, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 15H), 5.12 (s, 2H), 5.05 (d, *J* = 15.2 Hz, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 4.14 (d, *J* = 15.2 Hz, 1H), 3.98–3.93 (m, 2H), 3.84 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.08–3.03 (m, 1H), 2.72 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.66 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.35 (t, *J* = 6.8 Hz, 2H), 1.69–1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 160.9, 136.94, 136.83, 136.00, 128.65, 128.59, 128.49, 128.19, 128.12, 127.57, 127.55, 66.09, 62.6, 61.1, 54.1, 47.9, 46.5, 34.6, 34.0, 28.5, 28.3, and 24.6; ESI-MS *m*/*z* 515.2 $[M+H]^+$. Anal. Calcd for $C_{31}H_{34}N_2O_3S$: C, 72.34; H, 6.66; N, 5.44; S, 6.23. Found: C, 72.12; H, 6.47; N, 5.69; S, 6.54.

4.7. Benzyl(3a*S*,4*Z*,6a*R*)-5-(1,3-dibenzyl-2,3,3a,4,6,6a-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-5-ylidene) pentanoate 9

A mixture of **7** (5 g, 9.4 mmol), toluene (30 mL), and 18% HCl (20 mL) was stirred at 60 °C for 5 h. After being cooled to rt, the aq phase was extracted with toluene and the combined organic phase was washed with satd aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/hexane 1:2) to give **9** as a viscous oil (4.57 g, 95%). $[\alpha]_D^{25} = +154.4$ (*c* 1.0, MeOH); IR (neat): 3029, 2930, 1732, 1696, 1449, 1236, 1158, 1027, 746, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 15H), 5.39 (t, *J* = 6.8 Hz, 1H), 5.07 (s, 2H), 4.83 (d, *J* = 16.0 Hz, 1H), 4.75 (d, *J* = 15.2 Hz, 1H), 4.23–4.17 (m, 2H), 4.05–3.99 (m, 2H), 3.59–3.46 (m, 1H), 2.92 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.86 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.13–2.01 (m, 2H), 1.81–1.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 158.3, 137.4, 136.57, 136.49, 135.38, 128.06, 128.00, 127.87, 127.52, 127.40, 127.14, 126.97, 126.66, 124.88, 65.48, 64.04, 60.93, 58.41, 45.80, 44.36, 44.30, 36.47, 32.91, 30.37, 29.30, 28.52, and 23.50; ESI-MS *m*/*z* 513.4 $[M+H]^+$.

Anal. Calcd for $C_{31}H_{32}N_2O_3S$: C, 72.62; H, 6.29; N, 5.46; S, 6.25. Found: C, 72.45; H, 6.14; N, 5.31; S, 6.31.

4.8. Benzyl(3a*S*,4*S*,6a*R*)-5-(1,3-dibenzyl-2,3,3a,4,6,6a-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-5-yl)pentanoate 8

To a solution of **9** (2 g, 3.9 mmol), triethylsilane (1.36 g, 11.7 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (2.67 g, 23.4 mmol) dropwise at 0 °C. After the completion of addition, the mixture was allowed to rise to rt and stirred for 12 h. The reaction was quenched with saturated aq $NaHCO_3$ and then extracted with AcOEt, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/hexane 1:2) to give **8** as a viscous oil (1.84 g, 92%). The spectral properties of the product were identical to those of **8** obtained from **7**.

4.9. (+)-Biotin 1

A mixture of **8** (2.0 g, 3.89 mmol), 47% HBr (16 mL), and xylene (12 mL) was stirred at reflux for 36 h. After being cooled to rt, the aq phase was separated and concentrated under reduced pressure. To the residue, 21 mL 10% aq NaOH was added. The resulting solution was added dropwise to a mixture of triphosgene (1.15 g, 3.89 mmol), activated charcoal (0.02 g), and toluene (21 mL) at 25 °C. The mixture was stirred at the same temperature for 12 h and then filtered. The aq phase was acidified to pH 1 with concentrated aq HCl and cooled with ice water. The solid precipitated was collected and washed with water to give **1** as colorless crystals (0.76 g, 80%). Mp: 230–231 °C; $[\alpha]_D^{22} = +90.7$ (*c* 1.0, 0.1 M NaOH) (Lit.[6h] Mp: 231–233 °C; $[\alpha]_D^{22} = +91.2$ (*c* 1.0, 0.1 M NaOH)); IR (KBr): 3359, 3308, 2961, 2469, 1941, 1707, 1480, 1318, 1270, 1154, 1015, 842, 753, 651 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.9 (s, 1H), 6.40 (s, 1H), 6.33 (s, 1H), 4.30 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.15–4.11 (m, 1H), 3.12–3.07 (m, 1H), 2.82 (dd, *J* = 12.4, 5.2 Hz, 1H), 2.57 (d, *J* = 12.4 Hz, 1H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.62–1.41 (m, 4H), 1.37–1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 163.1, 61.5, 59.6, 55.8, 40.0, 33.9, 28.57, 28.52, and 25.0; ESI-MS *m*/*z* 267.2 $[M+Na]^+$.

4.10. X-ray crystallographic data of compound 3g

Crystals of compound **3g** suitable for X-ray analysis were obtained by recrystallization from ethyl acetate/cyclohexane (1:1) at room temperature. Crystallographic data (excluding structure factors) for the structure of **3g** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 683359. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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