Synthetic Studies on *d*-Biotin, Part 6:[1] An Expeditious and Enantiocontrolled Approach to the Total Synthesis of *d*-Biotin via a Polymer-Supported Chiral Oxazaborolidine-Catalyzed Reduction of *meso*-Cyclic Imide Strategy

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Dedicated with best wishes to Professor Zong-Ru Guo on the occasion of his 65th birthday.

Abstract: An efficient and highly enantioselective synthesis of *d*-biotin from the known *cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (**5**) was accomplished in 48% overall yield. The key reactions in the sequence involve the catalytic enantioselective reduction of *meso*-cyclic imide **6** using polymer-supported chiral oxazoborolidine, derived from (*S*)-α,α-diphenylprolinol and polymer-bound sulfonyl chloride, and the installation of the C_5 side chain at C4 in the thiolactone **9** via a Ni/C-catalyzed Fukuyama coupling reaction.

Key words: *d*-biotin, vitamin H, oxazaborolidine, polymer-supported chiral sulfonamide, enantioselective reduction, Fukuyama coupling reaction

Over the past five decades, interest in the total synthesis of *d*-biotin (**1**), a water-soluble vitamin, has increased as a result of its significant biological properties for human nutrition and animal health.[2] Though a number of synthetic strategies have been developed that make use of the resolution at an appropriate stage,[3] enantioselective syntheses[4] or starting from the chiral pool,[5] the first industrial method for the synthesis of **1** utilizing the (3a*S*,6a*R*)-thiolactone **9** as a key intermediate described by Goldberg and Sternbach at Hoffmann-La Roche in 1949, after subsequent modifications, still remains nowadays the most attractive and reliable approaches so far developed.[6] However, the potential of this Sternbach approach has not yet been fully realized due to the lack of an efficient and simple method for the desymmetrization of *meso* compounds such as dicarboxylic acid **5** and its imides **6** to prepare (3a*S*,6a*R*)-lactone **8**. As a result, the economy of this Sternbach process in today's market place leaves much to be desired, Herein we report an more economically efficient method for the synthesis of **1**, starting from the commercially available *cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (**5**), along the Sternbach's route by employing polymer- supported chiral oxazaborolidine-catalyzed asymmetric reduction of **6**.

Our synthetic route to **1** is outlined in Scheme 1. The essential steps in the present synthesis involve the enantioselective reduction of *meso*-cyclic imide **6** catalyzed by a polymer-supported chiral oxazaborolidine **13**, derived from (*S*)-α,α-diphenylprolinol and polymer-bound sulfonyl chloride, and the introduction of the C_5 side chain at C4 in the thiolactone **9** via a 5% Ni/C-catalyzed Fukuyama coupling reaction.[7]

The required zinc reagent **4** was prepared starting from 1,4-dibromobutane. The monobromo nitrile **2** was obtained in 80% yield upon treatment of 1,4-dibromobutane with NaCN in DMF using a modification of the procedure described by Voss et al.[8] Iodination of **2** in acetone gave the monoiodo nitrile **3** in 90% yield. The formation of zinc reagent with monoiodo nitrile, **3** was performed under modified Knochel's conditions[9] consisting of treatment of activated zinc powder in a mixture of TMSCl and THF. The reaction required 30 minutes at 30 °C for completion and afforded the zinc reagent **4**.

The *meso*-cyclic imide **6** was prepared in 95% yield by heating *cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (**5)** with benzylamine in the presence of 4 Å MS (molecular sieves) with azeotropic removal of water using a Dean–Stark apparatus, which provided better yields because the continuous removal of water forced the equilibrium toward the *meso*-cyclic imide **6**. It is noteworthy that xylene seems to be a better azeotropic agent than some others, such as toluene and benzene, etc., hence the removal of water was speedy.

With the *meso*-cyclic imide **6** in hand, our attention was turned to the development of an efficient asymmetric reduction of **6** to the (3a*S*,6*R*,6a*R*)-hydroxylactam **7** as precursor for the formation of (3a*S*,6a*R*)-lactone **8** to complete a formal catalytic asymmetric synthesis of **1**. Recently, Shimizu and co-workers have developed a highly enantioselective reduction of *meso*-cyclic *N*-benzylimides to chiral hydroxylactams with borane in the presence of oxazaborolidine, derived from L- threonine.[10] However, the recovery and purification of the catalyst are also problematic. Immobilization of chiral oxazaborolidine catalysts would offer a solution to the problem. Polymer-supported oxazaborolidine catalysts have wide uses in asymmetric organic synthesis owing to the ease of isolation of product from polymeric chiral catalyst, the convenient work-up procedure,[11] and the fact they can be recovered by filtration at the end of the reaction without loss of activity.[12] Thus, efforts were made to utilize polymer-supported chiral sulfonamide **13** (2.29 mmol/g, 200–400 mesh) as a catalyst for enantioselective reduction of

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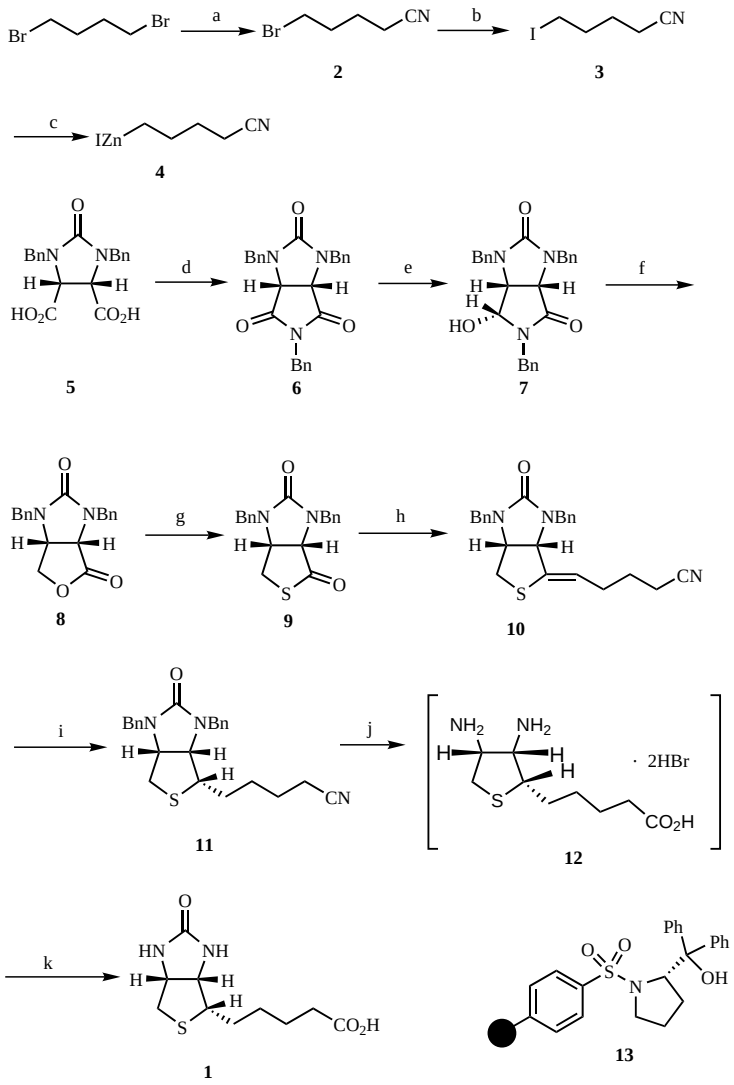

Scheme 1 *Reagents and conditions*: a) NaCN, DMF, 35 °C, 2 h, 80%; b) NaI, acetone, reflux, 6 h, 90%; c) Zn, TMSCl, THF, reflux, then **3**, 30 °C; d) $PhCH_2NH_2$, 4Å MS, xylene, reflux, 12 h 95%; e) **13**, $BH_3{\cdot}SMe_2$, THF, reflux, 6 h 91%; f) KBH_4, LiCl, THF, r.t., 6 h, then 1 N aq HCl, 55 °C, 30 min, 90% (two steps); g) EtSC(S)SK, DMF, 125 °C, 3 h, 93%; h) **4**, 5% Ni/C, toluene, THF, DMF, r.t., 30 h, 80% (two steps); i) H_2, $Pd(OH)_2$/C, EtOAc, 30 °C, 6 h 92%; j) 48% HBr, toluene, reflux, 40 h; k) triphosgene, aq 4 N NaOH, anisole, 6 h, then 2 N aq HCl 90% (from **11** to **1**)

6. The *meso*-cyclic imide **6** was reduced with $BH_3{\cdot}SMe_2$ in the presence of polymer-supported sulfonamide catalyst **13** under reflux for 6 hours. As expected, the reaction proceeded enantiosecletively to provide the (3a*S*,6*R*,6a*R*)-hydroxylactam **7** in 91% yield. The enantiomeric excess of **7** was determined to be >98.5% by chiral HPLC analysis. It is important to note that after the reduction was completed, the chiral polymer-supported sulfonamide could be recovered by simple filtration by first washing with refluxing methanol and then with hot water. Recycling of the catalyst was tested by the reduction of **6**. The results are summarized in Table 1. The results show that both enantiomeric excess and chemical yields gave reproducible values when the chiral polymeric catalyst was reused five times. The absolute configuration of **7** was confirmed both by its X-ray diffraction analysis (Figure 1) and by the observation of the coupling constant between C_6-H_{exo} and C_{6a}-H. The ^1H NMR data clearly indicated the stereochemistry at C-6. The coupling constant of 5.5 Hz between C_6-H_{exo} and C_{6a}-H shows that C_6-H_{exo} and C_{6a}-H are *syn*-disposed, and also the α-orientation of the C-6 hydroxy group.

Further reduction of **7** with KBH_4 in the presence of LiCl in THF at room temperature for 2 hours, followed by acid hydrolysis gave (3a*S*,6a*R*)-lactone **8** in 90% yield with 95% exantiomeric excess. It was enriched to 98.5% ee by recrystallization from ethanol. The conversion of **8** into the (3a*S*,6a*R*)-thiolactone **9** was carried out by a new method using potassium ethylthioxanthogenate EtSC(S)SK at 125 °C in DMF for 5 hours in 93% yield.

Having achieved construction of (3a*S*,6a*R*)-lactone **9** from **8** in excellent yield, we then proceeded to install the C_5 side chain to **9** using a modification of the Fukuyama

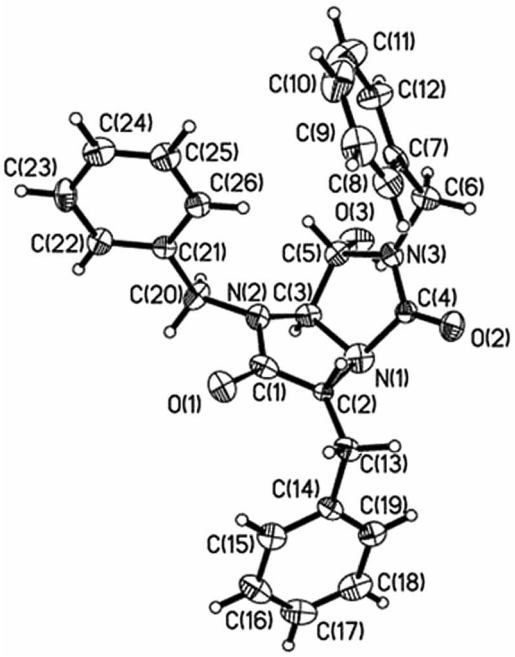

Figure 1 X-ray crystal structure of **7**

Table 1 The Recycling of the Chiral Polymer-Supported Sulfonamide in the Reduction of **6** in THF at Refluxing Temperature

Entry	Yield (%)[a]	Ee (%)
1	95.0	98.6
2	94.5	98.5
3	95.0	98.5
4	94.7	98.4
5	94.7	98.4

[a] Yields of isolated pure products.
[b] Determined by chiral HPLC analysis.

coupling procedure.[13] Treatment of **9** with **4** (1.5 equiv) in the presence of Ni/C in a mixed solvent of toluene, THF and DMF at room temperature for 30 hours provided the (*Z*)-vinyl nitrile **10** in 80% yield. The ^{1}H NOE experiments were carried out to assign the configuration of the double bond in **10** (Figure 2). An enhancement of 10.5% to the signal of the C_{3a}-H was observed when the olefinic hydrogen was irradiated, indicating the geometry of **10** is (*Z*)-configured.

Catalytic hydrogenation of **10** with a catalytic amount of $Pd(OH)_2$ on charcoal in EtOAc led stereospecifically to the saturated nitrile **11** in 92% yield. The absolute configuration of **11** was unambiguously confirmed by X-ray crystallographic analysis (Figure 3).

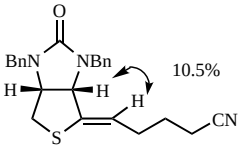

Figure 2 Significant NOE enhancement observed for **10**

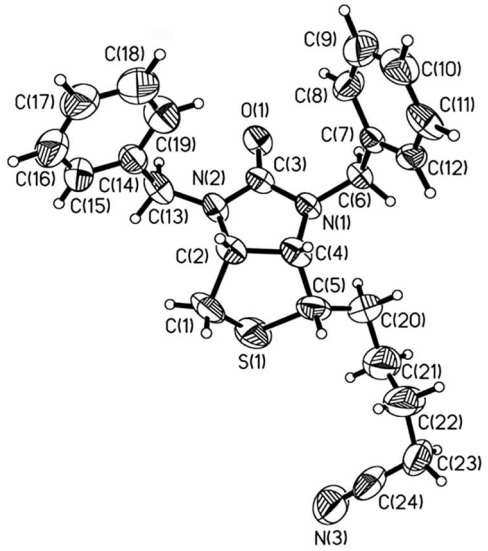

Figure 3 X-ray crystal structure of **11**

Finally, on refluxing **11** with 47% aq HBr, diamine·2HBr salt **12** was obtained in a one-pot debenzylation and hydrolysis and ring opening reaction which, without purification, was allowed to react with triphosgene in the presence of 4 N aq NaOH in anisole at 30 °C for 6 hours to afforded *d*-biotin (**1**) in 90% yield.

In conclusion, we have developed an efficient, asymmetric total synthesis of *d*-biotin in 48% overall yield, starting from commercially available 1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (**5**) by employing a polymer-supported chiral oxazaborolidine-catalyzed reduction of *meso*-cyclic imide **6** and a Ni/C-catalyzed Fukuyama coupling reaction to carry out the introduction of the C_5 side chain to the thiolactone **9**.

Melting points were determined on a WRS-1 digital melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Erba 1106 elemental analyzer. IR spectra were recorded on a Nicolet FI-IR 360 spectrometer. ^{1}H NMR spectra were obtained on a Bruker AMX × 300 spectrometer. Chemical shifts are reported relative to internal TMS. Mass spectra were measured on a HP-5988A spectrometer by direct inlet at 70 eV. HRMS were measured with EI techniques. Optical rotations were measured at r.t. (20 °C) on a Perkin-Elmer 241 MC polarimeter. Chiral HPLC analyses for the determination of enantiomeric purity of **9** were performed on a Shimadzu LC010AT provided with variable λ detector, working at λ = 254 nm and fitted with a Chiralcel OD column (25 × 0.46 cm). Conditions: hexane–propan-2-ol (6:4) as eluent, flow rate 0.6 mL/min. Unless otherwise stated, all chemicals were obtained from commercial suppliers and used without further purification. THF were freshly distilled from sodium benzophenone ketyl prior to use.

Polymer-supported chiral catalyst **13** was prepared according to the reported procedure.[14]

4-Bromovaleronitrile (2)

To a stirred solution of 1.4-dibromobutane (21.6 g, 0.1 mol) in DMF (100 mL) was added NaCN (4.9 g, 0.1 mol) and the reaction mixture was stirred for 2 h at 35 °C. After cooling to.r.t., the mixture was poured into H_2O (200 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with sat. aq NaCl (3 × 50 mL) and H_2O (3 × 40 mL) and dried (Na_2SO_4). Evaporation of the solvent and fractional distillation of the residue under reduced pressure afforded **2** (13.0 g, 80%) as a colorless oil; bp 118–121 °C/13 Torr (Lit.[8] bp 114–115 °C/12 Torr).

IR (film): 2213 cm^{-1} (C≡N).

^{1}H NMR ($CDCl_3$): δ = 3.37 (br t, 2 H, *J* = 7.1 Hz, CH_2Br), 2.66 (br t, 2 H, *J* = 7.0 Hz, CH_2CN), 1.79–2.29 (br m, 4 H, 2 × CH_2).

MS (EI): *m*/*z* (%) = 162 (M^+, 15.5), 82 (100), 55 (90), 54 (40).

4-Iodovaleronitrile (3)

To a stirred solution of **2** (16.2 g, 0.1 mol) in acetone (150 mL) was added NaI (19.5 g, 0.13 mol). The reaction mixture was stirred under reflux for 6 h. After cooling to r.t., the mixture was filtered through Celite and the filtrate was evaporated to remove the solvent. The residue was distilled under reduced pressure to afford **3** (18.8 g, 90%) as a pale yellow oil; bp 97–99 °C/1 Torr (Lit.[15] bp 98 °C/1 Torr).

IR (film): 2213 cm^{-1} (C≡N).

^{1}H NMR ($CDCl_3$): δ = 3.50 (br t, 2 H, *J* = 7.0 Hz, CH_2I), 2.64 (br t, 2 H, *J* = 7.0 Hz, CH_2CN), 1.78–2.28 (br m, 4 H, 2 × CH_2)

MS (EI): *m*/*z* (%) = 209 (M^+, 16.2), 127 (11.6), 82 (100), 55 (89), 54 (38).

***cis*-1,3-Dibenzyl-*N*-benzyl-2-imidazolidone-4,5-dicarboximide (6)**

A mixture of *cis*-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (**5**; 10 g, 28 mmol), benzylamine (3.3 g, 30.8 mmol), 4 Å MS (0.5 g), and xylene (75 mL) was refluxed using a Dean–Stark apparatus for 12 h. After cooling to r.t., the mixture was filtered to remove the molecular sieves and the filtrate was washed successively with 1 N aq HCl (3 × 25 mL), sat. aq NaCl (3 × 40 mL) and H_2O (3 × 35 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product, which was recrystallized from toluene to afford pure **6** (11.3 g, 95%) as a white solid; mp 114–116 °C.

IR (KBr): 3437, 1711, 1686, 1648 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.25 (s, 2 H, C_{3a}-H and C_{6a}-H), 4.26, 4.29, 4.73, 4.76 (4 d, 4 H, *J* = 15.38, 15.42, 2 × ArCH_2), 4.56 (s, 2 H, ArCH_2N), 7.18–7.36 (m, 15 H, 3 × C_6H_5).

MS (EI): *m*/*z* (%) = 425 (M^+, 26), 334 (3), 237 (7), 132 (12), 91 (100).

HRMS (EI): *m*/*z* calcd for $C_{26}H_{23}N_3O_3$: 425.4860; found: 425.4874.

Anal. Calcd for $C_{26}H_{23}N_3O_3$: C, 73.39; H, 5.45; N, 9.88. Found: C, 73.14; H, 5.40; N, 9.59.

(3a*S*,6*R*,6a*R*)-1,3,5-Tribenzyl-6-hydroxytetrahydro-4*H*-pyrrolo[3,4-*d*]imidazole-2,4(1*H*)-dione (7)

To a suspension of polymer-supported chiral catalyst **13** (6.1 g, 15 mmol) in THF (450 mL), was added dropwise a 2 M solution of BH_3·SMe_2 in THF (55 mL, 110 mmol). The suspension was refluxed with stirring under N_2 for 1 h, and then a solution of **6** (42.5 g, 100 mmol) in THF (180 mL) was added dropwise. The reaction mixture was refluxed with stirring for 6 h. After cooling to r.t., the mixture was treated with 0.5 N aq HCl (15 mL) and filtered. The polymeric catalyst was washed with EtOAc (3 × 25 mL) and H_2O (3 × 10 mL). The aqueous layer was extracted with EtOAc (3 × 40 mL) and then the combined organic layers were successively washed with H_2O (3 × 40 mL), sat. aq $NaHCO_3$ and sat. aq NaCl (3 × 40 mL), and dried (Na_2SO_4). Evaporation of the solvent gave the crude product, which was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give pure **7** (38.9 g, 91%) as a white solid; mp 128–131 °C; $[\alpha]_D^{20}$ +69.1 (*c* = 0.1, CH_2Cl_2).

IR (KBr): 3313, 2933, 1700, 1452, 1236, 1080, 740, 701 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.77–3.8 (m, 2 H, C_{3a}-H and C_{6a}-H), 4.90 (2 d, 1 H, *J* = 5.5 Hz, CHOH), 4.20, 4.40, 4.90, 4.93, 5.03, 5.12 (6 d, 6 H, 3 × ArCH_2), 7.21–7.40 (m, 15 H, 3 × ArH).

MS (EI): *m*/*z* (%) = 427 (M^+, 11), 264 (20), 106 (4), 91 (100).

Anal. Calcd for $C_{26}H_{25}N_3O_3$: C, 73.05; H, 5.89; N, 983. Found: C, 72.89, H, 5.65; N, 9.69.

MS (EI): *m*/*z* calcd for $C_{26}H_{25}N_3O_3$: 427.5018; found 427.4990.

(3a*S*,6a*R*)-1.3-Dibenzyltetrahydro-4*H*-furo[3,4-*d*]imidazole-2,4(1*H*)-dione (8)

To a stirred mixture of KBH_4 (26.9 g, 0.5 mol) and LiCl (2.12 g, 50 mmol) in THF (100 mL) was added dropwise a solution **6** (106.75 g, 0.25 mol) in THF (400 mL) at 10 °C. The reaction mixture was stirred at r.t. for 2 h, then 1 N aq HCl (150 mL) was added dropwise. The mixture was stirred at 55 °C for 30 min. After cooling to r.t., the mixture was extracted with EtOAc (4 × 80 mL) and the combined organic layers were washed with sat. aq NaCl (3 × 40 mL) and H_2O (3 × 40 mL), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by recrystallization from EtOH to afford pure **8** (72.5 g, 90%) as white needles; mp 117–119 °C $[\alpha]_D^{25}$ +59.3 (*c* = 1.0, $CHCl_3$){Lit.[3f] mp117–119 °C, $[\alpha]_D^{25}$ +59.2 (*c* = 1.0, $CHCl_3$)}.

IR (KBr): 1778, 1702, 1208, 1183, 1030, 968 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.24 (dd, 1 H, *J* = 2.3, 12.8 Hz, $CH_{exo}O$), 3.36 (dd, 1 H, *J* = 5.6, 12.8 Hz, $CH_{endo}O$), 3.95 (m, 1 H, *J* = 8.8 Hz, C_{3a}-H), 4.19 (3 d, 1 H, *J* = 2.3, 5.4, 8.0 Hz, C_{6a}-H), 4.25, 4.31, 4.47, 4.94 (4 d, 1 H, *J* = 14 Hz, 2 × ArCH_2), 7.28–7.37(m, 10 H, ArH).

MS (EI): *m*/*z* (%) = 322 (M^+, 24), 265 (55), 245 (78), 187 (60), 91 (100).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}N_2O_3$: 322.3466; found: 322.3487.

Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 70.81; H, 5.59; N, 8.70. Found: C 70.58, H 5.42, N 8.53.

(3a*S*,6a*R*)-1,3-Dibenzyltetrahydro-4*H*-thieno[3,4-*d*]imidazole-2,4(1*H*)-dione (9)

To a stirred solution of **8** (32.2 g, 0.1 mol) in DMF (200 mL) was added potassium ethylthioxanthogenate (17.6 g, 0.1 mol). The reaction mixture was stirred at 125 °C under N_2 for 3 h. After cooling to r.t., H_2O (150 mL) was added to the mixture before it was extracted with toluene (4 × 40 mL). The combined organic lagers were washed with sat. aq NaCl (3 × 40 mL) and H_2O (3 × 3 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude product obtained was purified by recrystallization from EtOAc to afford pure **9** (31.4 g, 93%); mp 125–126 °C $[\alpha]_D$ +90.2 (*c* = 1.0, $CHCl_3$) {Lit.[16] mp 125–127 °C $[\alpha]_D^{20}$ +90.8 (*c* = 1.0, $CHCl_3$)}.

IR (KBr): 1704, 1691, 1423, 1222 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.25 (dd, 1 H, *J* = 2.2, 12.8 Hz, $CH_{exo}S$), 3.36 (dd, 1 H, *J* = 5.5, 12.8 Hz, $CH_{endo}S$), 3.81 (d, 1 H, *J* = 8.0 Hz, C_{3a}-H), 4.15 (3 d, 1 H, *J* = 2.2, 5.5, 8.0 Hz, C_{6a}-H), 4.34, 4.37, 4.68, 5.01 (4 d, 4 H, *J* = 15.2 Hz, 2 ArCH_2), 7.28–7.35 (m, 10 H, ArH).

MS (EI): *m*/*z* (%) = 338 (M^+, 3), 310 (23), 277 (7), 264 (68), 91 (100).

Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 67.46; H, 5.33; N, 8.28; S, 9.47. Found: C, 67.23; H, 5.23; N, 8.12; S, 9.31.

(3a*S*,6a*R*)-1,3-Dibenzyltetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one-4-ylidenepentane Nitrile (10)

To a stirred suspension of activated zinc powder (23 g, 0.35 mol) in THF (55 mL) was added 1, 2-bromoethane (1.75 g, 9.3 mmol). The reaction mixture was stirred under reflux for 15 min. After cooling to r.t., TMSCl (0.69 g, 6.4 mmol), was added, and the slurry was stirred at r.t. for 20 min. Compound **3** (37.6 g, 0.18 mol) was then added, and the mixture was stirred at 30 °C to give a solution of the zinc regent **4** in THF. To this stirred solution of **4** in THF was added **9** (20 g, 59.2 mmol), 5% Ni/C (1.8 g), toluene (60 mL) and DMF (5 mL) and stirring was continued for 30 h at r.t. The mixture was filtered through Celite. The catalyst was washed with toluene (3 × 20 mL) and the combined organic layers were evaporated under reduced pressure. The residue was dissolved in Et_2O (150 mL) and the solution was washed successively 1 N aq HCl (3 × 30 mL) sat. aq $NaHCO_3$ (4 × 30 mL) and sat. aq NaCl (3 × 25 mL) and dried (Na_2SO_4). Evaporation of the solvent gave the crude product, which was purified by chromatography on a silica gel column (hexane–EtOAc, 3:1) to afford pure **10** (19.1 g, 80%) as a colorless oil; $[\alpha]_D^{20}$ +27.4 (*c* = 0.1, CH_2Cl_2).

IR (Film): 2224 (C≡N) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.39–1.86 (m, 4 H, 2 × CH_2), 2.03 (t, 2 H, CH_2CN), 2.81 (2 × d, 1 H, *J* = 5.5, 12.2 Hz, $CH_{exo}S$), 2.95 (d, 1 H, *J* = 12.3 Hz, $CH_{endo}S$), 4.13 (m, 1 H, C_{6a}-H), 4.67 (d, 1 H, *J* = 7.9 Hz, C_{3a}-H), 4.05, 4.34, 4.51, 4.96 (4 × d, 4 H, *J* = 15.5, 16.8, Hz, 2 × ArCH_2).

MS (EI): *m*/*z* (%) = 404 (M^+, 7), 313 (62), 106 (10), 91 (100).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{25}N_3OS$: 403.7279; found: 403.7251.

Anal, Calcd for $C_{24}H_{25}N_3OS$: C, 71.43; H, 6.24; N, 10.41. Found: C, 71.54; H, 6.33; N, 10.28.

(3a*S*,4*S*,6a*R*)-1,3-Dibenzyltetrahydro-1*H*-thieno[3,4-*d*]imidazole-2(3*H*)-one-4-ylpentane Nitrile (11)

A suspension of Pd $(OH)_2$/C (1.5 g) in EtOAc (100 mL) was preactivated under a hydrogen pressure of 4 atm for 1.5 h. A solution of **10** (20.2 g, 50 mmol) in EtOAc (120 mL) was added. The reaction mixture was shaken at 30 °C under 4 atm hydrogen pressure for 6 h, and then filtered through Celite. The filtrate was evaporated under reduced pressure to give the crude product, which was purified by recrystallization from *i*-PrOH to afford pure **11** (18.7 g, 92%) as a white solid; mp 93–94 °C, $[\alpha]_D^{25}$ –67.3 (*c* = 1.02, DMSO).

IR (KBr): 2270 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.58–1.75 (m, 6 H, 3 × CH_2), 2.34 (t, 2 H, *J* = 6.56 Hz, CH_2CN), 2.71 (4 d, 2 H, *J* = 2.34, 4.39 Hz, C_{6a}-H and C_6-H), 3.06 (m, 1 H, C_4-H), 3.89 (dd, 1 H, *J* = 5.56 Hz, C_{3a}-H), 3.96 (m, 1 H, C_{6a}-H), 4.03, 4.15, 4.75, 5.00 (4 d, 4 H, *J* = 15.07, 15.0 Hz, 2 × C$H_2C_6H_5$), 7.22–7.38 (m, 10 H, 2 × C_6H_5).

EI-MS: *m*/*z* (%) = 405 (M^+, 18), 91 (100), 277 (48), 187 (21), 314 (20), 278 (17), 265 (16), 264 (14).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{26}N_3OS$: 404.5549; found: 404.5561.

Anal. Calcd for $C_{24}H_{26}N_3OS$: C, 71.11; H, 64.20; N, 9.38. Found: 7.90 C, 71.27; H, 61.83; N, 9.26; S, 7.79.

***d*-Biotin (1)**

A mixture of **11** (40.4 g, 0.1 mol), 47% aq HBr (200 mL) and toluene (20 mL) was refluxed with vigorous stirring for 40 h. After cooling to r.t., the organic layer was separated. The aqueous layer was extracted with toluene (3 × 40 mL) and evaporated under reduced pressure. A solution of NaOH (40 g, 0.1 mol) in H_2O (245 mL) was added to the residue and the stirring was continued for 25 min at r.t. A solution of triphosgene (59.4 g, 0.2 mol) in anisole (300 mL) was added, and the reaction mixture was stirred at 30 °C for 6 h. The mixture was controlled to keep pH of the solution within 8–9 by addition of 4 N aq NaOH. The mixture was diluted with H_2O (150 mL) and extracted EtOAc (4 × 40 mL). The aqueous layer was acidified to pH 2 with 2 N aq HCl with stirring to give a precipitate. The precipitated product was collected by filtration, and recrystallized from H_2O to afford pure **1** (22 g, 90%) as a white crystalline powder; mp 231–232 °C, $[\alpha]_D^{25}$ +91.2 (*c* = 1.0, 0.1 N NaOH) {Lit.[4g] mp 232–233 °C, $[\alpha]_D^{22}$ +91.2 (*c* = 1.0, 0.1 N NaOH)}.

IR (KBr): 3311, 2933, 1705, 1665 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.30–1.61 (m, 6 H, 3 × CH_2), 2.17 (t, 2 H, *J* = 7.3 Hz, CH_2CO_2H), 2.58 (dd, 1 H, *J* = 1.7, 12.5 Hz, $CH_{endo}S$), 2.80 (dd, 1 H, *J* = 4.7, 12.5 Hz, $CH_{exo}S$), 3.14 (m, 1 H, C_4-H), 4.17 (m, 1 H, C_{3a}-H), 4.36 (m, 1 H, C_{6a}-H), 6.37 (s, 1 H, NH), 6.47 (s, 1 H, NH), 11.98 (br s, 1 H, CO_2H).

EI-MS: *m*/*z* (%) = 245 (M^+ + 1, 15), 227 (9), 184 (25), 112 (26), 97 (100), 85 (66).

Anal. Calcd for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.47; S, 13.12. Found: C, 49.01; H, 6.49; N, 11.50; S, 13.40.

X-Ray Structure Analysis of 7

Crystals of $C_{26}H_{25}N_3O_3$ (427.50) suitable for X-ray analysis were obtained from EtOAc. A colorless monoclinic crystal of dimensions 0.40 × 0.30 × 0.30 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 $P2_1,2_1,2_1$ with *a* = 10.910 (6), *b* = 9.189 (6), *c* = 10.949 (4) Å; β = 104.87 (4)° *Z* = 2; *V* = 1060.9 (10)Å^3; μ(Mo-*Ka*) = 0.089 mm^{-1}; *Dc* = 1.338 gcm^{-3}; *F*(000) = 452 reflections were collected in the range of 1.92° < < 25.17 using Mo-Kα radiation (graphite monochromator, λ = 0.71073 Å), ω-2θ scan mode. The structure was solved by direct methods and expanded using difference Fourier techniques and refined by full-matrix, least-square to *R* = 0.0811, R_ω = 0.1905 with ω = 1/[$\sigma^2(F_o)$ + (0.1035 P^2 + 1.3711 P) R (where $P = (F_o^2 + 2F_c^2)/3$) by using the 1232 observed reflections having I > 2.00σ(I) for 284 paremeters refined. All non-hydrogen atoms were refined anisotropically.

X-Ray Structure Analysis of 11

Crystals of $C_{24}H_{26}N_3OS$ (404.54) suitable for X-ray analysis were obtained from EtOAc. A colorless orthorhombic crystal of dimensions 0.20 × 0.20 × 0.30 mm was mounted on a Rigaku AFC7R diffractometer. Determination of the cell parameters was performed by least squares refinement of 28 reflections. The compound crystallized in the monoclinic system, space group $P2_12_12_1$ with *a* = 9.6929 (4), *b* = 11.059 (4), *c* = 42.0841(17) Å; *Z* = 8; *V* = 4511.2 (3) Å^3; μ(Mo-*Ka*) = 0.162 mm^{-1}; *Dc* = 1.191 gcm^{-3}; *F* (000) = 1720 reflections were collected in the range of 1.90 < θ < 28.30° using Mo-Kα radiation (graphite monochromator, λ = 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* = 0.0675, R_ω = 0.1766 with ω = 1/[$\sigma^2(F_o)$ + (0.1035 P^2 + 1.3711 P) R (where $P = (F_o^2 + 2F_c^2)/3$) by using the 10576 observed reflections having I > 2.00σ(I) for 533 parameters refined. All non-hydrogen atoms were refined anisotropically.

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