An Efficient and Enantioselective Synthesis of *d*-Biotin

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Received 12 May 2000; revised 14 August 2000

Dedicated with best wishes to Professor Qi-Zhuo Wang on the occasion of his 80th birthday

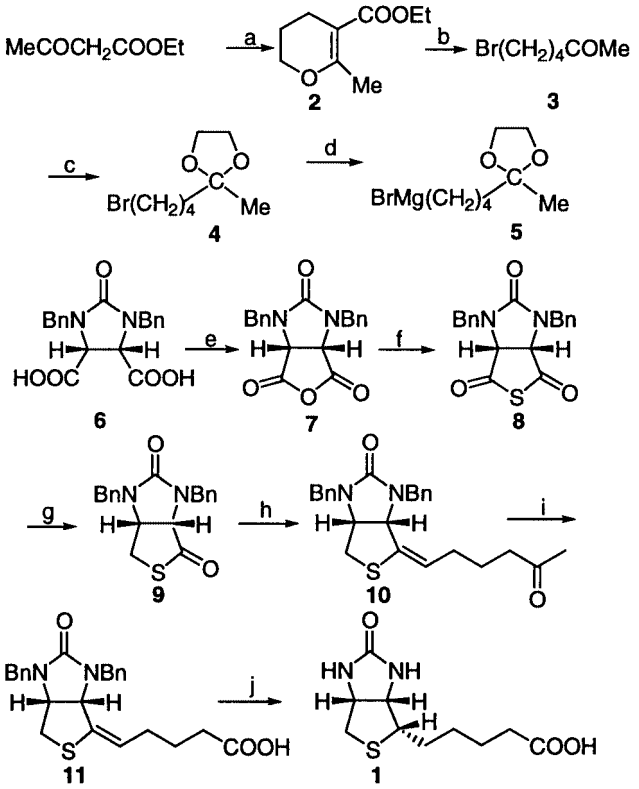
Abstract: An efficient and enantioselective synthesis of *d*-biotin **1** starting from *cis*-1,3-dibenzyl-2-imidazo-lidone-4,5-dicarboxylic acid (**6**) is described. The key steps are the enantioselective reduction of *meso*-1,2-dicarboxylic thioanhydride **8** to prepare the (3a*S*, 6a*R*)- thiolactone **9** and the introduction of the C_6 side chain at C-2 in **9** via a modified Grignard reaction. This novel synthesis proceeded in six steps to afford **1** with 21% overall yield.

Key words: *d*-biotin, vitamin H, (*R*)-BINAL-H, enantioselective reduction, Grignard reaction

Since its isolation from beef liver in 1941,[1] *d*-biotin referred to as vitamin H has attracted considerable attention as a favorite target for total synthesis[2] due to its applications in human and animal nutrition, as well as the study of biosynthetic pathways.[3] To date, a number of new synthetic routes involving different strategies for control of the three adjacent chiral centres have been reported.[4] However, to the best of our knowledge, none of the known syntheses appears to have a commercial advantage over the long used Sternbach synthesis developed at Hoffmann−La Roche Company.[5] Although the Sternbach synthesis continues to provide **1** on a large scale, there are still many disadvantages that either involve an intermediate resolution with possible recycling or require a comparative large number of reaction steps to carry out the introduction of the pentanoate side chain to the (3a*S*, 6a*R*)-thiolactone **9**. As a consequence, simpler and more economical synthetic routes, with fewer reaction steps would be desirable. Described herein is a practical and enantioselective process for synthesis of **1,** from the known *cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxy-lic acid (**6**).[6]

The synthetic route to **1** is outlined in the Scheme. The requisite C_6 unit **5** was prepared from ethyl acetoacetate and 1-bromo-3-chloropropane by successive cyclization, decarboxylation-opening/bromination, ketalization[7] and Grignard reagent formation. On the other hand, the commercially available *cis*-1,3-dibenzyl-2-imidazoli-done-4,5-dicarboxylic acid (**6**) was converted to the known *meso*-cyclic-1,2-dicarboxylic anhydride **7** in 98% yield using a modification of the procedure by described by Gerecke et al.[8]

Reaction of **7** with sodium sulfide (2:1 molar ratio) in a mixed THF/H_2O solvent system at room temperature led to the *meso*-thioanhydride **8** in almost quantitative yield (based on moles of sodium sulfide), with approx. 50% recovery of **6**.



Reagents and conditions: (a) 1-bromo-3-chloropropane, K_2CO_3, toluene, 80 °C, 94%; (b) 47% HBr, NaBr, H_2SO_4, 50 °C, 86%; (c) $(CH_2OH)_2$, TsOH, toluene, reflux, 92%; (d) Mg, THF, r.t.; (e) Ac_2O, cat. 85% H_3PO_4, reflux, 98%; (f) $Na_2S{\cdot}9H_2O$, THF, H_2O, r.t., 49%; (g) (*R*)-BINAL-H, THF, −78 °C to r.t., 83%; (h) **5**, THF, reflux, then 30% H_2SO_4, 60 °C, 82%; (i) I_2, KI, 10%NaOH, dioxane, 60 °C, 75%; (j) HCO_2H, CH_3SO_3H, 10% Pd/C, reflux, 85%

Scheme

Enantioselective reduction of *meso*-cyclic-1,3-dicarboxylic anhydrides with two carbon centres of opposite chirality with lithium aluminum hydride-ethanol-1,1′-bi-2-naphthol complex (BINAL-H) provides useful chiral building blocks for the preparation of a wide variety of optically active compounds[9] such as (3a*S*, 6a*R*)-1,3-dibenzyl-tetrahydro-4*H*-furo[3,4-*d*]imidazole-2,4-(1*H*)-dione, a key intermediate for *d*-biotin synthesis. The high enantioselectivity obtained by this methodology associated with its operational simplicity encouraged us to use it as a way to introduce asymmetry into our synthetic approach. Following this procedure, the enantioselective reduction **8** with 3 molar amounts of (*R*)-BINAL-H[10] in THF at

−78°C, followed by gradual warming to room temperature and treatment with 10% HCl afforded the desired (3a*S*,6a*R*)-thiolactone **9** in 83% yield. The optical purity of **9** was determined to be 98.5%ee by HPLC analysis using a chiral stationary phase. A decrease in optical purity (88%ee) was observed when the reaction was carried out at −40 °C to room temperature overnight in an attempt to drive the reaction to completion. The structure and absolute configuration was confirmed by comparison with the ^{1}H NMR spectrum of **9**, prepared from (3a*S*, 6a*R*)-1,3-dibenzyl-tetrahydro-4*H*-furo[3,4-*d*]imidazole-2,4(1*H*)-dione according to Gerecke's procedure[8] and was further supported by the X-ray crystallographic data (Figure 1)

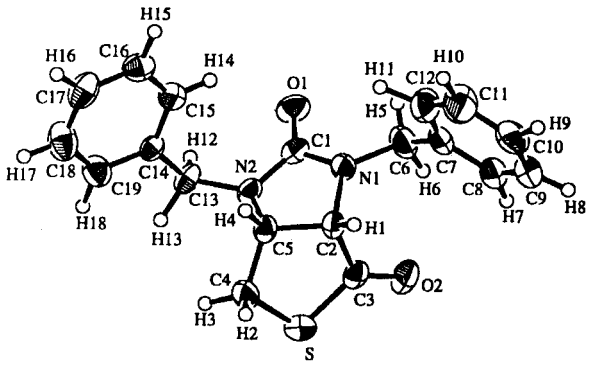


Figure 1 X-ray crystal structure of **9**

In addition, the transition state model proposed by Matsuki et al.[9] to account for the highly enantioselective reduction *meso*-cyclic carboxylic acid derivatives with (*R*)-BINAL-H can equally be used to interpret the high enantioselectivity observed for **9**. Between the two possible transition states **A** and **B**, the transition state **A** should be more favorable electronically owing to the n/π^* attractive orbital between the oxygen non-bonding orbital and the LUMO of thioanhydride moiety in comparison with transition state **B** that has a repulsive interaction between the oxygen non-bonding orbital and the HOMO of urea moiety (Figure 2). Thus, (*R*)-BINAL-H is positioned to attack the carbonyl carbon attached to the *R*-center of the *meso* -thioanhydride **8** via the transition state **A** rather than the carbonyl carbon attached to *S*-center of **8**, leading to the (3a*S*, 6a*R*)-hydroxythiolactone, which after further reduction with an excess of (*R*)-BINAL-H and acidic workup affords the predominating enantiomer (3a*S*, 6a*R*)-thiolactone **9**.

The C_6 side chain was introduced by the addition of an excess of Grignard reagent **5** to **9** in THF at reflux, followed by dehydration and hydrolysis with 30% H_2SO_4 at 60 °C in a one-pot procedure to afford the (E)-alkene **10** in an 82% overall yield. The E geometry of **10** was unambiguously assigned both by its X-ray structure analysis (Figure 3) and by observation of resonance associated with the olefinic methine center. The ^{1}H NMR spectrum exhibited a triplet at δ = 5.42 ppm (J = 7.2 Hz) for the olefinic methine of the side chain. These values are in good agreement with those observed in its analogs **11** with an E configuration.

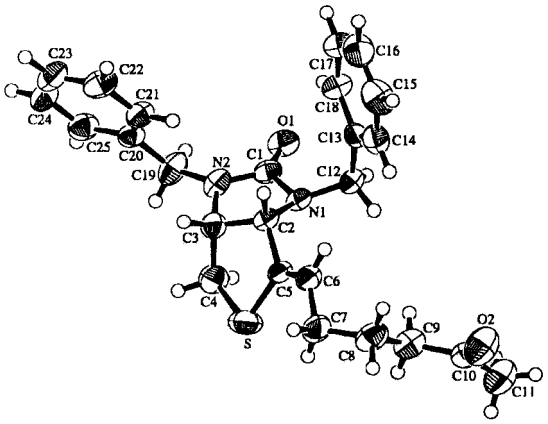


Figure 3 X-ray crystal structure of **10**

After oxidative degradation of the methyl ketone group in **10** by NaOI, formed in situ from iodine and dilute aqueous NaOH in the presence of KI in dioxane at 60 °C, the carboxylic acid **11** was obtained in 75% yield. As expected, its specific rotation was consistent with that in the literature.[12] The remaining steps were the reduction of carbon-carbon double bond and debenzylation. The transforma-

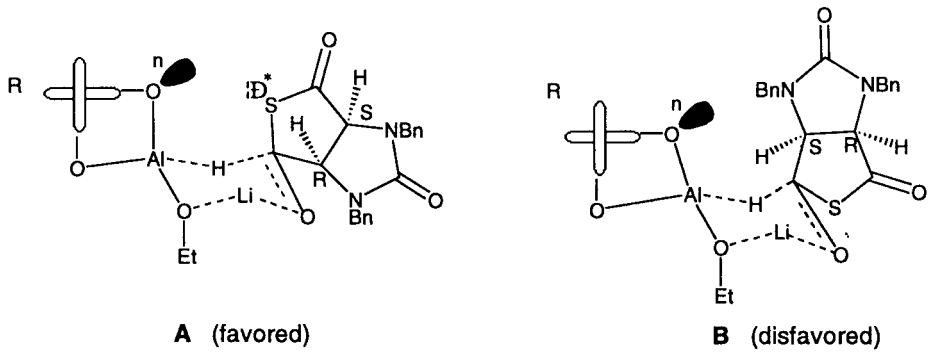


Figure 2 Proposed transition states for the formation of **A** and **B**

tion of **11** into **1** has been carried out by catalytic hydrogenation of the double bond of **11** with 10% palladium on charcoal followed by debenzylation with 48% aqueous HBr[13] or methanesulfonic acid[14] in a two-step procedure. It was considered that these two steps could be accomplished in a single vessel. Indeed, treatment of **11** with formic acid and methanesulfonic acid in the presence of 10% palladium on charcoal at reflux provided the desired *d*-biotin (**1**) in 85% yield, which was found identical in every respect with authentic material from Aldrich Chemical Company.

In conclusion, a practical and high-yielding total synthesis of *d*-biotin **1** from *cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (**6**) was accomplished via the expeditious enantioselective reduction of *meso*-1,2-dicarboxylic-thioanhydride and modified Grignard reaction as key reaction steps. This method is expected to have the potential for production of *d*-biotin **1**.

Mps were determined on a WRS-1 digital melting point apparatus and are uncorrected. Elemental analyses were performed on a CarloErba 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 recorded on a HP 5988A instrument by direct inlet at 70 eV. 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 LC-10AT provided with variable λ detector, working at λ = 254 nm and fitted with a Chiralcel OD column (25 × 0.46 cm). Conditions: hexane/2-propanol (6:4) as eluent, flow rate 0.5mL/min. Unless otherwise stated, all chemicals were obtained from commercial suppliers and used without further purification. THF were freshly distilled from sodium benzophenone ketyl immediately prior to use.

cis-1,3-Dibenzyl-tetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (7)

A mixture of **6** (35.4 g, 0.1 mol), Ac_2O (28.4 mL, 0.3 mol) and 85% H_3PO_4 (1 g) was stirred under reflux for 2 h. After cooling to r.t., the precipitate was filtered and washed with H_2O to give **7** (33.0 g, 98%) as a white solid.

mp: 236−238 °C (Lit.[6] mp: 236−237 °C).

IR (KBr): ν = 1805, 1740, 1687, 1227 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.21 (s, 2H, C_{3a}-H and C_{6a}-H), 4.19 (d, 2H, *J* = 15.0 Hz, $ArCH_2$), 5.10 (d, 2H, *J* = 15.0 Hz, $ArCH_2$), 7.26−7.39 (m, 10H, ArH).

MS (EI): *m/z* (%) = 336 (M^+,13.6), 264 (15.6), 173 (5.8), 132 (11), 91 (100).

Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.87; H, 4.76; N, 8.33. Found: C, 67.51; H, 4.45; N, 8.03.

cis-1,3-Dibenzyl-tetrahydro-2*H*-thieno[3,4-*d*]imidazole-2,4,6-trione (8)

A mixture of **7** (33.6 g, 0.1 mol), $Na_2S{\cdot}9H_2O$ (12 g, 0.05 mol), THF (100 mL) and H_2O (100 mL) was stirred at r.t. for 3 h. The reaction mixture was poured into EtOAc (350 mL) and separated. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with sat. brine, dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product, which was recrystallized from EtOH/H_2O to afford pure **8** (8.65 g, 49% based on $Na_2S{\cdot}9H_2O$ used) as a white solid.

mp: 140−142 °C.

IR (KBr): ν = 1763, 1726, 1685, 1585 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.15 (s, 2H, C_{3a}-H and C_{6a}-H), 4.19 (d, 2H, *J* = 15.0 Hz, $ArCH_2$), 5.13 (d, 2H, *J* = 15.0 Hz, $ArCH_2$), 7.26−7.37(m, 10H, 2 × ArH).

MS (EI): *m/z* (%) = 352 (M^+,0.43), 264 (47.3), 173 (4), 91(100).

Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.55; N, 7.95; S, 9.09. Found: C, 63.92; H, 4.27; N, 7.60; S, 8.89.

HRMS: *m/z* Calcd for $C_{19}H_{16}N_2O_3S$: 352.4058. Found: 352.4079.

The aqueous layer was acidified to pH 2 with 10% HCl solution to permit facile recovery of the diacid **6** (17.5 g, 49% based on **7**) as a pale yellow solid; mp: 170−172 °C (Lit.[15] mp: 170−171 °C).

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

To a stirred suspension of $LiAlH_4$ (11.4 g, 0.3 mol) in anhydrous THF (100 mL) at 0 °C under N_2 atm was added anhyd EtOH (17.5 mL, 0.3 mol) in anhyd THF (100 mL). After 10 min, a solution of (*R*)-(+)-1,1′-bi-2-naphthol (85.9 g, 0.3 mol) in anhyd THF (150 mL) was added dropwise at 0 °C and the reaction mixture was stirred at r.t. for 2.5 h. After this time, the mixture was cooled to −78 °C and **8** (35.2 g, 0.1 mol) in anhyd THF (100 mL) was added to the reaction mixture over 25 min. Stirring was maintained at −78 °C for a further 6 h, then gradually warmed to r.t. 10% HCl (150 mL) was added dropwise under ice cooling and extracted with $CHCl_3$ (3 × 70 mL). The combined organic layers were washed with 10% Na_2CO_3 (3 × 70 mL) and H_2O (3 × 25 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the crude product, which was recrystallized from EtOAc to afford pure **9** (28.0 g, 83%) as a white solid.

mp: 125−127 °C; $[\alpha]_D$ = +89.5° (*c* 1.0, $CHCl_3$) {Lit.[16] mp: 125−126°C, $[\alpha]_D$ = +90.8° (*c* 1.0, $CHCl_3$)}; ee 98.5%.

IR (KBr): ν = 1704, 1684, 1420, 1225 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.28 (dd, 1H, *J* = 2.2, 12.45 Hz, $CH_{endo}S$), 3.38 (dd, 1H, *J* = 5.5, 12.5 Hz, $CH_{exo}S$), 3.82 (d, 1H, *J* = 7.9 Hz, C_{3a}-H), 4.14 (m, 1H, C_{6a}-H), 4.36, 4.37, 4.69, 5.04 (4 × d, 4H, *J* = 15.2 Hz, 2 × $ArCH_2$), 7.28−7.35 (m, 10H, ArH).

MS (EI): *m/z* (%) = 338 (3), 310 (20), 277 (5), 264 (66), 187 (38), 91 (100).

Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.46; H, 5.33; N, 8.28; S, 9.47. Found: C, 67.20; H, 5.18; N, 8.09; S, 9.27.

The aqueous layer was acidified to pH 3−4 with 5% HCl and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with sat. brine and dried (Na_2SO_4). After removing the solvent, the residue was recrystallized from benzene to give pure (81.6 g, recovery 95%) of (*R*)-(+)-1,1′-bi-2-naphthol as a white solid.

Mp: 207−208 °C; $[\alpha]_D^{20}$ = +35° (*c* 1.0, THF) {Lit.[17] mp: 206−207 °C, $[\alpha]_D^{20}$ = +35.2° (*c* 1.0, THF)}.

(3a*S*,6a*R*)-1,3-Dibenzyl-4-(5-oxo-hexylidene)-tetrahydro-1*H*-thieno[3,4-*d*]imidazole-2(3*H*)-one (10)

To a stirred solution of Grignard reagent **5**, [prepared from **4** (22.3 g, 0.1 mol) and Mg (2.9 g, 0.12 mol) in anhyd THF(140 mL) with stirring at reflux for 1.5 h under N_2 atm] after addition of a catalytic amount of I_2, was added a solution of **9** (13.3 g, 0.04 mol) in anhyd THF (120 mL) dropwise at 15 °C over 1 h. The mixture was stirred at reflux overnight and then allowed to cool to r.t. 30% H_2SO_4 (80 mL) and THF (80 mL) were added and the mixture was refluxed with stirring for 2 h. After cooling, the mixture was quenched by the addition of H_2O (180 mL) and extracted with

EtOAc (3 × 100 mL). The combined organic layers were washed several times with sat. brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow oil, which was purified by chromatography (EtOAc/hexane, 5:9) on a silica gel column to afford pure **10** (13.8 g, 82%) as a white solid.

mp: 50−52 °C; $[\alpha]_D$ = +208.7° (*c* 1.0, $CHCl_3$).

IR (KBr): ν = 1708, 1645, 1419, 1237 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.61−2.06 (m, 4H, 2 × CH_2), 2.13 (s, 3H, CH_3CO), 2.39 (t, 2H, *J* = 7.3 Hz, CH_2CO), 2.72 (d, 1H, *J* = 12.6 Hz, $CH_{endo}S$), 2.93 (dd, 1H, *J* = 5.3, 12.6 Hz, $CH_{exo}S$), 4.08 (m, 1H, C_{6a}-H), 4.28 (d, 1H, *J* = 7.7 Hz, C_{3a}-H), 4.05, 4.22, 4.82, 4.95 (4 × d, 4H, *J* = 15.3, 15.7 Hz, 2 × $ArCH_2$), 5.42 (t, 1H, *J* = 7.2 Hz, CH), 7.27−7.31 (m, 10H, 2 × ArH).

MS (EI): *m/z* (%) = 420 (M^+, 4), 363 (2), 329 (9), 238 (6), 187 (3), 91 (100).

Anal. Calcd for $C_{25}H_{28}N_2O_2S$: C, 71.43; H, 6.67; N, 6.67; S, 7.62. Found: C, 71.21; H, 6.49; N, 6.43; S, 7.43.

HRMS: *m/z* Calcd for $C_{25}H_{28}N_2O_2S$: 420.5675. Found: 420.5659.

(3a*S*,6a*R*)-1,3-Dibenzyl-tetrahydro-1*H*-thieno[3,4-*d*]-imidazole-2(3*H*)-one-4-ylidenepentanoic Acid (11)

To a stirred solution of I_2 (10 g, 39.4 mmol) and KI (7 g, 45 mmol) in H_2O (50 mL) was added dropwise 10% NaOH (100 mL). After 30 min, a solution of **10** (15 g, 35.7 mmol) in freshly distilled dioxane (260 mL) was slowly added, and the mixture was stirred at 60 °C for 2 h. After cooling to r.t., the mixture was filtered and the solid material (iodoform) was washed with H_2O (100 mL). The filtrate was treated with 5% Na_2SO_3 (30 mL) in order to destroy the excess NaOI and then acidified to pH 2 with 15% HCl with stirring. The precipitated product was collected by filtration, washed with H_2O, and recrystallized from *i*-PrOH/hexane to give pure **11** (11.3 g, 75%) as a white solid.

mp: 83−85 °C; $[\alpha]_D^{20}$ = +236.2° (*c* 1.0, 0.1 N NaOH) {Lit.[12] mp: 84−85 °C, $[\alpha]_D$ = +236.2° (*c* 1.0, 0.1 N NaOH)}.

IR (KBr): ν = 3432, 1725, 1662, 1485, 1452 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.39−1.93 (m, 4H, 2 × CH_2), 2.00 (t, 2H, *J* = 7.4 Hz, CH_2CO), 2.81 (dd, 1H, *J* = 5.5, 12.1 Hz, $CH_{exo}S$), 2.95 (d, 1H, *J* = 12.3 Hz, $CH_{endo}S$), 4.16 (m, 1H,C_{6a}-H), 4.62 (d, 1H, *J* = 7.9 Hz, C_{3a}-H), 4.05, 4.34, 4.52,4.97(4 × d, 4H, *J* = 15.5, 16.8 Hz, 2 × $ArCH_2$), 5.56 (t, 1H, *J* = 7.8 Hz, CH), 7.24−7.40 (m, 10H, 2 × ArH).

MS (EI): *m/z* (%) = 422 (M^+, 6), 311 (6), 91 (100).

Anal. Cacld for $C_{24}H_{26}N_2O_3S$: C, 68.25; H, 6.16; N, 6.63; S, 7.58. Found: C, 68.43; H, 5.91; N, 6.63; S, 7.36.

***d*-Biotin 1**

To a stirred suspension of **11** (42.2 g, 0.1 mol) and 10% Pd/C (15 g) in formic acid (150 mL) was added methanesulfonic acid (150 mL) in a single portion, and the mixture was stirred at reflux for 15 h. After cooling to 50 °C, the catalyst was filtered off. The filtrate was poured into H_2O (350 mL) with stirring to give a precipitate, which was recrystallized from H_2O to yield pure **1** (20.8 g, 85%) as a white crystalline powder.

mp: 232−233 °C; $[\alpha]_D$ = +91.2° (*c* 1.0, 0.1 N NaOH) {Lit.[18] mp: 229.5−230 °C, $[\alpha]_D^{25}$ = +91.3° (*c* = 1.0, 0.1 N NaOH)}.

IR (KBr): ν = 3305−3245, 2705−2500, 1705, 1665 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.31−1.60 (m, 6H, 3 × CH_2), 2.18 (t, 2H, *J* = 7.3 Hz, CH_2COOH), 2.59 (dd, 1H, *J* = 1.7, 12.5 Hz, $CH_{endo}S$), 2.81 (dd, 1H, *J* = 4.7, 12.5 Hz, $CH_{exo}S$), 3.15 (m, 1H, $C_{4β}$-H), 4.18 (m, 1H, C_{3a}-H), 4.35 (m, 1H, C_{6a}-H), 6.35 (s, 1H, NH), 6.48 (s, 1H, NH), 11.99 (br s, 1H, COOH).

MS (EI): *m/z* (%) = 245 (M^++1, 15), 227 (8), 199 (1), 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, 48.97; H, 6.45; N, 11.52; S, 13.39.

X-Ray Structure Analysis of 9

Crystals of $C_{19}H_{18}N_2O_2S$ (338.42) suitable for X-ray analysis were obtained from EtOH. A colorless prismatic 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 19 reflections. The compound crystallizes in the orthorhombic system, space group $P2_12_12_1$(No.19) with *a* = 12.010(3), *b* = 17.993(2), *c* = 7.895(2) Å; *Z* = 4; *V* = 1698.2 (6) $Å^3$ 3; *u*(Mo-Kα) = 2.04 cm^{-1}; *Dc* = 1.324 gcm^{-3}; *F*(000) = 712. 2262 reflections were collected in the range 18.45<2*c*<24.18°, using Mo-Kα radiation (graphite monochromator, λ = 0.71069 Å), ω-2*c* scan mode. The structure was solved by direct method (SHELXS86)[19] and expanded using Fourier techniques[20] and refined by full-matrix least-square to *R* = 0.042 and R_w = 0.048 with $\omega = 1/\sigma^2(F_o)$ by using the 1657 observed reflections having I>2.00σ(I) for 218 parameters refined. All non-hydrogen atoms were refined anisotropically.

X-Ray Structure Analysis of 10

Crystals of $C_{25}H_{28}N_2O_2S$ (420.57) suitable for X-ray analysis were obtained from EtOAc. A colorless prismatic 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 23 reflections. The compound crystallizes in the orthorhombic system, space group $P2_12_12_1$(No.19) with *a* = 9.379(5), *b* = 41.524(5), *c* = 5.666(7) Å; *Z* = 4; *V* = 2206(2) $Å^3$; *u*(Mo-Kα) = 1.71 cm^{-1}; *Dc* = 1.266 gcm^{-3}; *F*(000) = 896. 3006 reflections were collected in the range 14.39<2*c*<21.71°, using Mo-Kα radiation (graphite monochromator, λ = 0.71069 Å), ω-2*c* scan mode. The structure was solved by direct method (SHELXS86)[19] and expanded using Fourier techniques[20] and refined by full-matrix least-square to *R* = 0.055 and R_w = 0.058 with $\omega = 1/\sigma^2(F_o)$ by using the 1670 observed reflections having I>2.00σ(I) for 272 parameters refined. All non-hydrogen atoms were refined anisotropically.

Acknowledgement

This work was supported by a Grant-in-Aid (96107) for Scientific Research from the Ministry of Chemical Industry of China. We also gratefully acknowledge Prof. Xiang-Jun Li for helpful comments and suggestions.

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Article Identifier:
1437-210X,E;2000,0,14,2004,2008,ftx,en;F02600S.pdf