A Novel Synthesis of a Key Intermediate for (+)-Biotin from L-Aspartic Acid

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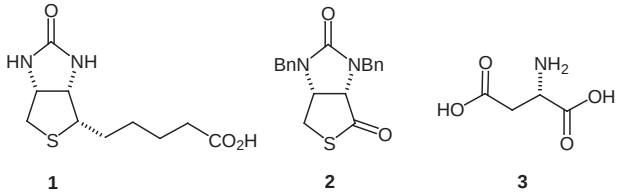
Received 30 October 2001; revised 7 December 2001

Abstract: The aldol reaction of an *N*-Cbz-3-amino-4-butanolide **4**, derived from L-aspartic acid, with formaldehyde gave the *trans*-disubstituted 3-amino-4-butanolide **5** stereoselectively. Following protection of the hydroxyl group of **5**, amidation and oxidation provided the β-substituted L-asparagine derivative **6**. The Hofmann rearrangement of **6** with sodium hypochlorite in the presence of sodium hydroxide and subsequent hydrogenation gave the bicyclic lactone **11**, which upon dibenzylation and thionation, gave the thiolactone **2**, a key intermediate for the synthesis of (+)-biotin (**1**).

Key words: vitamins, stereoselective synthesis, amino acids, aldol reaction, rearrangement

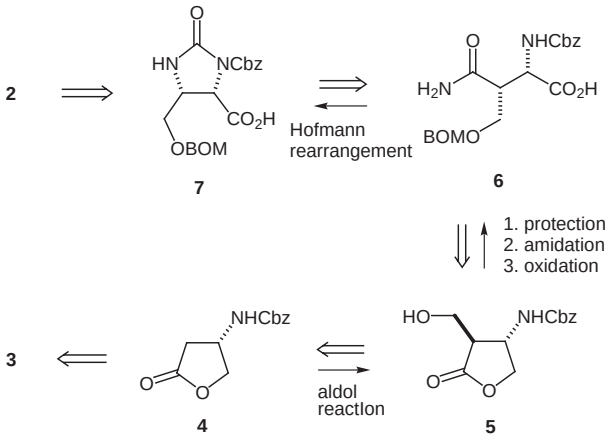
(+)-Biotin (**1**) is a water-soluble vitamin isolated in 1941[1] and has received much attention as a synthetic target because of its useful biological properties for human nutrition and animal health.[2] Since the first total synthesis of **1** was accomplished about fifty years ago, a number of synthetic routes have been devised.[3] Among them, the method utilizing the thiolactone **2** as a key intermediate is considered to be one of the most expedient approaches to **1**. Some practical synthetic methods of **2** have been developed, which involve the ones based on diastereomeric[4] or enzymatic resolution,[5] chiral pool method with L-cysteine as a starting material,[6] and asymmetric synthesis.[7] However, no approach starting from readily accessible L-aspartic acid has been reported. As a part of our synthetic studies utilizing L-aspartic acid (**3**) as a starting material for biologically active compounds,[8] we report herein a novel synthesis of **2** from **3** (Figure 1).



1 2 3

Figure 1

We envisioned the synthetic route outlined in Scheme 1. The required consecutive asymmetric centers at C-3a and C-6a of (+)-biotin (**1**) were planned to be set by stereoselective introduction of a hydroxymethyl group at C-2 of the *N*-Cbz-3-amino-4-butanolide **4** derived from **3**. The imidazolidin-2-one moiety of (+)-biotin (**1**) might be formed by the Hofmann rearrangement of the protected amide **6**, which is obtained from the lactone **5** through protection of the hydroxyl group, ring-opening with ammonia and oxidation of the hydroxymethyl group. Removal of the protective groups of the resultant imidazolidin-2-one derivative **7** and subsequent dibenzylation and thionation should give the desired thiolactone **2**.



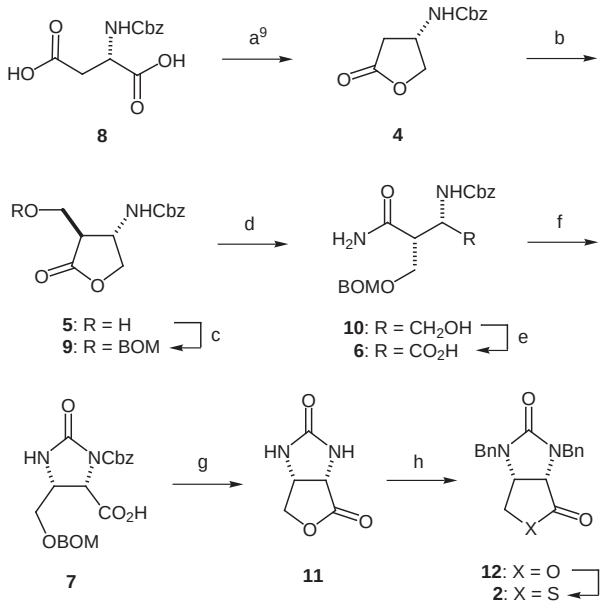
Scheme 1

The *N*-Cbz-3-amino-4-butanolide **4** was prepared according to the literature[9] from *N*-Cbz-L-aspartic acid **8** through formation of an acid anhydride followed by regioselective reduction of the α-aminocarbonyl group (Scheme 2). Yoda and co-workers have reported a stereoselective hydroxymethylation at C-2 of an (*S*)-*N*-Boc-3-amino-4-butanolide.[10] The method was applied to the Cbz derivative **4** to provide the desired *trans*-disubstituted *N*-Cbz-3-amino-4-butanolide **5** with a high stereoselectivity (*trans*/*cis* = 12:1). The diastereoselectivity was determined by the ^{1}H NMR spectrum. The enantiomeric integrity of **5** is assured because the reactions of electrophiles with dianions generated from *N*-Cbz-3-amino-4-butanolide derivatives have been reported to proceed without any racemization.[11] The hydroxyl group of **5** was protected as a benzyloxymethyl ether (BOM ether) and was allowed to react with aqueous ammonia in methanol to provide the amide alcohol **10**. The Hofmann rearrangement of **10** failed because of the poor solubility. We thus decided to use the acid derivative **6** with higher solubility than **10**. Oxidation of the hydroxymethyl group of **10** was conducted using Jones' reagent to give the acid **6**. Treatment of **6** with aqueous sodium hypochlorite in the presence of so-

Synthesis 2002, No. 3, 18 02 2002. Article Identifier:
1437-210X,E;2002,0,03,0361,0364,ftx,en;F08301SS.pdf.

ISSN 0039-7881

dium hydroxide[12] expectedly resulted in a clear solution. Upon stirring at 55 °C for 50 minutes, a clean rearrangement and a spontaneous cyclization took place to give the desired cyclic urea **7** in good yield. The *cis* configuration of **7** is ensured because the Hofmann rearrangement proceeds with retention of the configuration.[12] Removal of the protective groups of **7** by hydrogenation provided the bicyclic lactone **11**. The structure of **11** was confirmed by an X-ray crystallographic analysis (Figure 2).[13] The compound **11** was treated with benzyl bromide in the presence of sodium hydride followed by heating with potassium thioacetate in DMF[4a] providing the desired thiolactone **2** in good yield (Scheme 2). The product **2** obtained by the present method revealed its identity with an authentic sample with respect to mp, IR, ^{1}H NMR, mass spectra and specific rotation[14] {mp 122–123 °C; $[\alpha]_D^{25}$ +90.5 (*c* = 1.0, $CHCl_3$)}{Lit.[4a] mp 125–127 °C; $[\alpha]_D^{25}$ +91.3 ± 0.9 (*c* = 1.0, $CHCl_3$)}.



Scheme 2 *Reagents and conditions*: a: i) Ac_2O, ii) $NaBH_4$, THF, iii) HCl, 95%; b: i) LDA, THF, ii) HCHO, –78 °C, 62%, *trans*/*cis* = 12:1; c: BOMCl, *i*-Pr_2NEt, THF, quant.; d: NH_4OH, MeOH, 58%; e: Jones' reagent, acetone, 76%; f: NaOCl, NaOH, H_2O, 70%; g: H_2, $Pd(OH)_2$/C, MeOH, 80%; h: BnBr, NaH, DMF, 84%; i: AcSK, DMF, 92%

In conclusion, a novel synthesis of the (+)-biotin key intermediate **2** from L-aspartic acid was accomplished. The compound **2** was synthesized in 11% overall yield and in 9 steps from readily accessible *N*-Cbz-L-aspartic acid **8**. As the compound **2** has been converted to (+)-biotin (**1**) in 3 steps by our reported procedure,[15] (+)-biotin (**1**) is now accessible in 12 steps from **8**. The present method is efficient in terms of ready availability of the starting material and high stereoselectivities of the aldol reaction and the Hofmann rearrangement to form the required consecutive chiral centers. The present synthetic scheme would enable access to a variety of (+)-biotin analogs, which would have interesting biological properties.

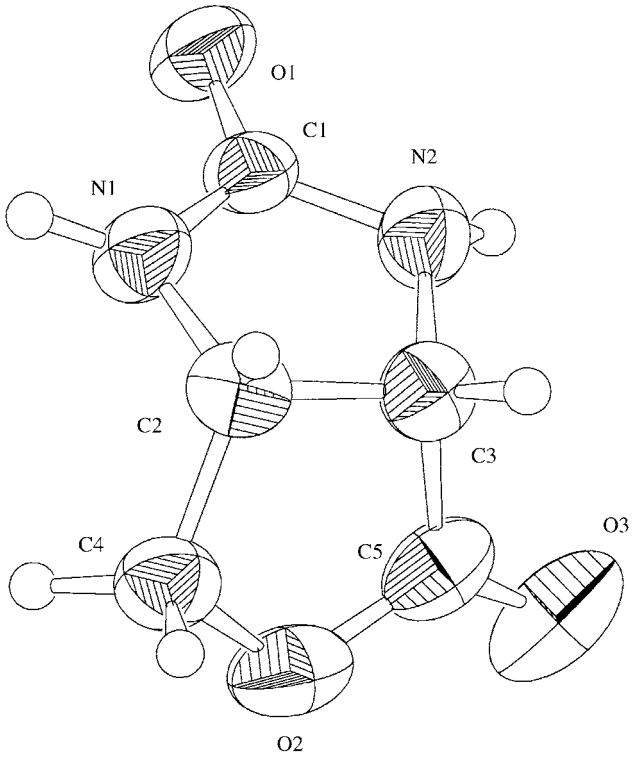


Figure 2 ORTEP II Diagram of Compound **11**[13]

Melting points are uncorrected. ^{1}H NMR spectra were recorded with tetramethylsilane as an internal standard. Optical rotations were measured at the indicated temperature with a sodium lamp (D line, 589 nm). Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). THF was distilled from sodium/benzophenone ketyl. Other solvents and reagents were used as received.

(2*R*,3*S*)-3-Benzyloxycarbonylamino-2-hydroxymethyl-4-butanolide (5)

To a solution of *i*-Pr_2NH (33 mL) in THF (90 mL) was added BuLi (1.6 mol/L in hexane, 150 mL, 0.24 mol) at –78 °C under N_2 and the mixture was stirred at 0 °C for 15 min. To the resulting solution was added **4** (21 g, 89 mmol) in THF (180 mL) at –78 °C and the mixture was stirred at the same temperature for 1 h. Monomeric formaldehyde solution was prepared according to the literature[16] by using paraformaldehyde (20.3 g), *p*-toluenesulfonic anhydride (3.3 g) and THF (450 mL), and was added dropwise to the enolate solution at –78 °C. The mixture was stirred at –78 °C for 1 h. To the mixture was added 10% aq citric acid (500 mL) and the mixture was extracted with EtOAc. The extracts were washed with H_2O, dried ($MgSO_4$) and evaporated. The residue (*trans*/*cis* = 12:1, determined from the ^{1}H NMR spectrum: The C-2 proton of the *trans*-isomer appeared at δ = 2.70–2.75 and that of *cis*-isomer at 2.82–2.87) was purified by silica gel column chromatography (hexane–EtOAc–$CHCl_3$, 1:1:1) and subsequent crystallization by adding *i*-Pr_2O to give **5** (14.7 g, 62%) as colorless crystals; mp 89–92 °C; $[\alpha]_D^{20}$ –1.3 (*c* = 1.0, MeOH).

IR (KBr): 3316, 1765, 1703 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.30–7.40 (m, 5 H), 5.15–5.21 (br, 1 H), 5.11 (s, 2 H), 4.40–4.62 (m, 2 H), 3.92–4.13 (m, 3 H), 2.70–2,75 (m, 1 H).

SIMS: *m*/*z* = 266 (M^+ + 1).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.92; H, 5.37; N, 5.42.

(2*R*,3*S*)-3-Benzyloxycarbonylamino-2-benzyloxymethoxy-methyl-4-butanolide (9)

To a solution of **5** (2.96 g, 11.2 mmol) in THF (60 mL) were added *i*-Pr_2NEt (8.8 mL, 50.4 mmol) and BOMCl (3.5 mL, 25.5 mmol) at 10 °C, and the mixture was stirred at 10 °C for 1 h and at 25 °C for 2 h. The mixture was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 10:1 to 4:1 to 2:1) to give **9** (4.5 g, quant.) as a colorless oil; $[\alpha]_D^{20}$ –2.6 (*c* = 0.9, MeOH).

IR (Nujol): 3335, 1782, 1721 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.26–7.52 (m, 10 H), 5.10–5.20 (m, 3 H), 4.62–4.75 (m, 2 H), 4.53–4.62 (m, 3 H), 4.41–4.45 (m, 1 H), 3.87–3.98 (m, 3 H), 2.69–2.79 (m, 1 H).

SIMS: *m*/*z* = 386 (M^+ + 1).

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.10; H, 6.32; N, 3.26.

(2*R*,3*S*)-3-Benzyloxycarbonylamino-2-benzyloxymethoxy-methyl-4-hydroxy-butanamide (10)

To a solution of **9** (1.64 g, 4.3 mmol) in MeOH (33 mL) was added concd aq NH_3 (8.4 mL) at 10 °C and the mixture was stirred at 20 °C for 2 h. The mixture was evaporated and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 7:1) to give **10** (989 mg, 58%) as colorless crystals; mp 165–168 °C; $[\alpha]_D^{20}$ –8.3 (*c* = 0.18, MeOH).

IR (KBr): 1688, 1660 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.43 (s, 1 H), 7.29–7.36 (m, 10 H), 7.12 (d, *J* = 7.6 Hz, 1 H), 6.95 (s, 1 H), 5.01 (s, 2 H), 4.59–4.64 (m, 2 H), 4.43–4.51 (m, 2 H), 3.65–3.72 (m, 2 H), 3.56–3.59 (m, 1 H), 3.15–3.42 (m, 3 H), 2.51–2.65 (m, 1 H).

SIMS: *m*/*z* = 403 (M^+ + 1).

Anal. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.69; H, 6.51; N, 6.96. Found: C, 62.72; H, 6.71; N, 6.82.

(2*S*,3*R*)-3-Aminocarbonyl-2-benzyloxycarbonylamino-4-benzyloxymethoxybutanoic Acid (6)

To a solution of **10** (697 mg, 1.73 mmol) in acetone (7 mL) was added dropwise Jones' reagent [prepared from CrO_3 (3.5 g), H_2O (25 mL) and conc. H_2SO_4 (3.05 mL), 4.2 mL] over 1 h at 10 °C. The excess reagent was destroyed by adding *i*-PrOH and the mixture was diluted with EtOAc. The mixture was washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was crystallized by adding *i*-Pr_2O to give **6** (548 mg, 76%) as colorless crystals; mp 124–126 °C; $[\alpha]_D^{20}$ –14.4 (*c* = 0.1, MeOH).

IR (KBr): 1693, 1652 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 12.4–12.7 (br s, 1 H), 7.56 (d, *J* = 9.6 Hz, 1 H), 7.47 (s, 1 H), 7.27–7.36 (m, 10 H), 6.93 (s, 1 H), 4.96–5.05 (m, 2 H), 4.59–4.64 (m, 2 H), 4.37–4.51 (m, 3 H), 3.64–3.71 (m, 2 H), 2.92–2.97 (m, 1 H).

SIMS: *m*/*z* = 417 (M^+ + 1).

Anal. Calcd for $C_{21}H_{24}N_2O_7$: C, 60.57; H, 5.81; N, 6.73. Found: C, 60.41; H, 6.01; N, 6.80.

(4*R*,5*S*)-1-Benzyloxycarbonylamino-4-benzyloxymethoxy-methylimidazolidin-2-one-5-carboxylic Acid (7)

To a solution of 0.1 mol/L aq NaOH (2.4 mL, 0.24 mmol) was added **6** (100 mg, 0.24 mmol) followed by aq NaOCl (8 wt%) (290 mg, 0.312 mmol) at 10 °C. The mixture was stirred at 10 °C for 1 h and at 55 °C for 50 min. The mixture was acidified by adding 1 N aq HCl and extracted with EtOAc. The extracts were washed with H_2O, dried ($MgSO_4$) and evaporated to give **7** (69.6 mg, 70%) as a colorless oil; $[\alpha]_D^{20}$ –3.1 (*c* = 0.4, MeOH).

IR (Nujol): 1782, 1738 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.26–7.39 (m, 10 H), 5.64 (s, 1 H), 5.12–5.30 (m, 2 H), 4.77 (d, *J* = 9.7 Hz, 1 H), 4.74 (s, 2 H), 4.58 (s, 2 H), 4.05–4.11 (m, 1 H), 3.79–3.82 (m, 1 H), 3.44–3.49 (m, 1 H).

SIMS: *m*/*z* = 415 (M^+ + 1).

Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35; N, 6.76. Found: C, 61.21; H, 5.45; N, 6.99.

(3a*S*,6a*R*)-Tetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (11)

A mixture of **7** (100 mg, 0.24 mmol), 10% $Pd(OH)_2$/C (dry) (20 mg) in MeOH (1 mL) and H_2O (0.2 mL) was hydrogenated in Parr apparatus at r.t. for 17 h under 3.5 kg/cm^2 of H_2. The mixture was filtered and the filtrate was evaporated. The residue was crystallized by adding MeOH and Et_2O to provide **11** (27 mg, 80%) as colorless crystals; mp 159–161 °C; $[\alpha]_D^{20}$ +62.0 (*c* = 1.0, MeOH).

IR (KBr): 3246, 1777, 1691 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.11–4.17 (m, 1 H), 4.29–4.48 (m, 3 H), 6.85 (s, 1 H), 7.37 (s, 1 H).

SIMS: *m*/*z* = 143 (M^+ + 1).

Anal. Calcd for $C_5H_6N_2O_3$: C, 42.26; H, 4.26; N, 19.71. Found: C, 42.44; H, 4.12; N, 19.69.

(3a*S*,6a*R*)-1, 3-Dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (12)

To a suspension of NaH (63.7% in mineral oil, 113 mg, 3 mmol) in DMF (2 mL) were added **11** (142 mg, 1 mmol) and benzyl bromide (0.36 mL, 3 mmol) at 0 °C and the mixture was stirred at r.t. for 17 h. To the mixture was added H_2O and the product was extracted with EtOAc. The combined extracts were washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was crystallized by adding Et_2O and hexane to afford **12** (271 mg, 84%) as colorless crystals; mp 120–121 °C (Lit.[4a] mp 120–121 °C). $[\alpha]_D^{20}$+58.0 (*c*, 1.0, benzene) {Lit.[4a] $[\alpha]_D^{20}$+58.2 (*c*, 1.0, benzene)}.

IR (KBr): 1775, 1706 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.23–7.40 (m, 10 H), 5.06 (d, *J* = 16 Hz, 1 H), 4.64 (d, *J* = 16 Hz, 1 H), 4.38 (d, *J* = 16 Hz, 1 H), 4.35 (d, *J* = 16 Hz, 1 H), 4.03–4.17 (m, 3 H), 3.92 (d, *J* = 8 Hz, 1 H).

SIMS: *m*/*z* = 323 (M^+ + 1).

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

The compound **2** was synthesized in 92% yield from **12** according to the known procedure;[4a] mp 122–123 °C (Lit.[4a] mp 125–127 °C); $[\alpha]_D^{25}$ +90.5 (*c* = 1.0, $CHCl_3$) {Lit.[4a] $[\alpha]_D^{25}$ +91.3 ± 0.9 (*c* = 1.0, $CHCl_3$)}. Optical purity: >99% ee [HPLC: CHIRALPAK AD, hexane–EtOH (85:15), 225 nm, 40 °C, 0.8 mL/min].

IR (KBr): 1696, 1680 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.09–7.45 (m, 10 H), 5.04 (d, *J* = 16 Hz, 1 H), 4.69 (d, *J* = 16 Hz, 1 H), 4.32–4.40 (m, 2 H), 4.09–4.17 (m, 1 H), 3.81 (d, *J* = 8 Hz, 1 H), 3.24–3.43 (m, 2 H).

SIMS: *m*/*z* = 339 (M^+ + 1).

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