Facile Synthesis of L-3,4-Didehydrovaline Constituting an Antibiotic, Phomopsin A

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Abstract: A convenient synthesis of β,γ-unsaturated valine (L-3,4-didehydrovaline), an important constituent of an antibiotic phomopsin A, was achieved from H-D-Ser-OH through a seven-step conversion in 31% overall yield.

Key words: didehydrovaline, deprotection, Jones' oxidation, β-elimination, Grignard reaction, amino acids

Antibiotic phomopsin A (**1**),[1,2] isolated from the culture of *Phomopsis leptostromifomis*, has a unique hexapeptide consisting of two parts. The natural product **1** features a very interesting main cyclodidehydrotripeptide called Fragment A and linear didehydrotripeptide called Fragment B as the exocyclic substructure, as illustrated in the Figure.

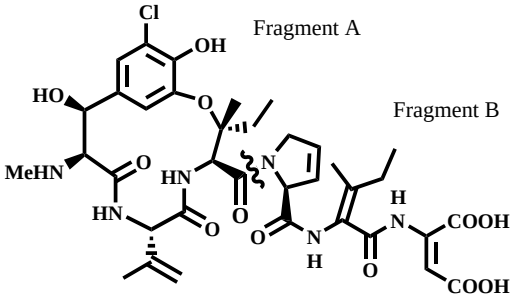
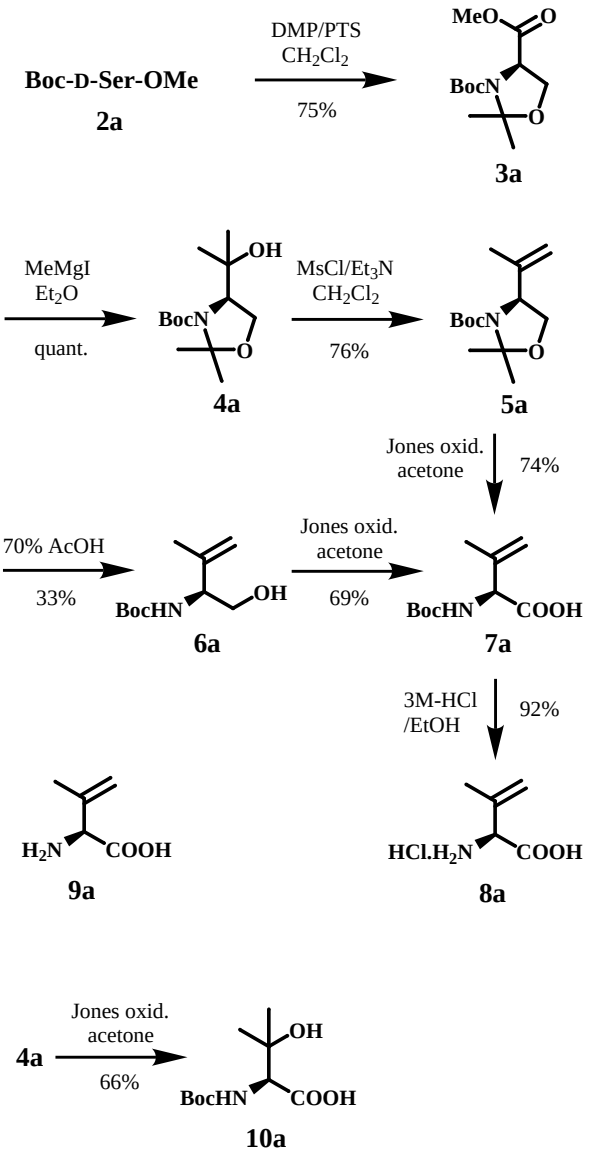


Figure Structure of Phomopsin A (**1**).

The above-mentioned Fragment A is entirely constituted of unusual α-amino acid moieties, 2-amino-3-methylbut-3-enoic acid [(*S*)-3,4-didehydrovaline, H-L-3-ΔVal-OH)] (**9a**), (2*S*,3*S*)-hydroxyisoleucine, and (2*S*,3*S*)-3-hydroxy-2-(*N*-methyl)tyrosine derivatives. Recently, besides the novel syntheses[3,4] of (*E*)-2,3-didehydroaspartic acid (ΔAsp), (*E*)-2,3-didehydroisoleucine (ΔIle) and 3,4-didehydroproline (ΔPro) constructing the Fragment B, we have already reported briefly the syntheses of a variety of the related didehydrooligopeptides as well.[5,6] At present, the synthesis of each moiety of the cyclopeptide segment has been carried out; in particular, the convenient synthesis of **9** is thought to be very essential. Furthermore, interestingly, the β,γ-unsaturated α-amino acids, including **9**, have potent biological activity,[7] both as enzyme inhibitors[8–10] and as antibiotics.[11] So far, the synthesis of **9** has been already reported in racemic form by three independent groups,[12–14] although the racemic form has been resolved only by using hogacylase.[15] Here, we wish to report the facile syntheses of (*S*)- and (*R*)-H-3-ΔVal-OH•HCl (**8a** and **8b**) from D- and L-H-Ser-OH, respectively, in seven steps (Scheme).



Scheme

First of all, *N*-*tert*-butoxycarbonyl (Boc)-D-Ser-OMe (**2a**), derived by the protection of H-Ser-OMe with di-*tert*-butyl dicarbonate (Boc_2O), was further protected with 2,2-dimethoxypropane (DMP) to give methyl (4*R*)-3-Boc-2,2-dimethyl-1,3-oxazolidine-4-carboxylate (**3a**).[16] Subsequently, Grignard reaction of **3a** with MeMgI in diethyl ether at 0 °C proceeded smoothly to give (4*S*)-4-(1-hydroxy-1-methylethyl)-3-Boc-2,2-dimethyl-1,3-oxazolidine (**4a**) almost quantitatively. Then, β-elimination of **4a** with methanesulfonyl chloride (MsCl) in the presence of Et_3N in CH_2Cl_2 at −10 °C gave (4*S*)-4-(1-methylethenyl)-3-Boc-2,2-dimethyl-1,3-oxazolidine (**5a**), the isopropylidene (Ip) group of which was deprotected with 70% AcOH to give the corresponding 2-aminobutenol derivative **6a**. Subsequent Jones' oxidation of **6a** was performed to give (2*S*)-2-(*N*-Boc)amino-3-methylbut-3-enoic acid (Boc-L-3-ΔVal-OH) (**7a**) in 69% yield. However, unfortunately, the yield of **6a** from **5a** was found to be markedly low (33%). Accordingly, an alternative direct synthetic method from **5a** to **7a** was tried successfully. Namely, in this case, the simultaneous deprotection and oxidation of **5a** using excess Jones' reagent in acetone was carried out to give the expected **7a** in 74% yield. The Boc group of **7a** was deprotected with 3 M HCl to give **8a** in 92% yield, as shown in the Scheme. Quite similarly, the synthesis of **8b** has been also successful from H-L-Ser-OH (**2b**). The melting points and the specific rotations of **8a** and **8b** were identical to those of the authentic samples derived by the resolution of the racemic form.[15] Furthermore, the aqueous solution of both hydrochlorides have been readily neutralized to pH 6 with 1 M LiOH to give the expected **9a** and **9b**, respectively.[15]

In addition, convenient synthesis of L-2-(*N*-Boc)-3-hydroxyvaline (**10**), which is an important and unusual α-amino acid constituent of a macrocyclic antibiotic, berninamycin A,[17] was achieved by oxidation of **4a** with Jones' reagent in acetone at 0 °C.

In conclusion, the facile and convenient syntheses of L-, D-3-ΔVal-OH and 3-hydroxy-Val-OH were accomplished by simple reactions using readily accessible D- and L-H-Ser-OH, respectively. In particular, simultaneous deprotection and oxidation of **5** and **4** with Jones' reagent to **7** and **10**, respectively, was found to be very effective.

Melting points were determined with Yamato Mp-21 melting points apparatus, and are uncorrected. The IR spectra were recorded on a Hitachi 270-30 spectrometer in KBr. The ^1H NMR spectra were measured with a JEOL EX 270 spectrometer in $CDCl_3$ solution with TMS as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH (Japan Spectroscopic Co., Ltd.).

Methyl (4*R*) and (4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidine-4-carboxylates (3a and 3b)

To a stirred solution of Boc-D-Ser-OMe (**2**, 17.9 g, 81.5 mmol) in CH_2Cl_2 (100 mL) were added DMP (50 mL, 410 mmol) and *p*-toluenesulfonic acid monohydrate (1.6 g, 8.2 mmol) at 0 °C. After stirring at r.t. for 12 h, the mixture was poured into aq sat $NaHCO_3$ solution (100 mL) and then the resulting solution was extracted with Et_2O (3 × 60 mL). The organic layer was washed with aq satd $NaHCO_3$ solution (3 × 50 mL), brine (3 × 50 mL), and then dried (Na_2SO_4). Concentration in vacuo gave a crude oil, which was distilled in vacuo to give **3a** as a colorless oil; yield: 16.5 g (76%); bp 111−113 °C/4 Torr; $[\alpha]_D^{25}$ +54.5 (*c* =1.0, $CHCl_3$). {Lit.[16] bp 101−102 °C/2 Torr; $[\alpha]_D$ +53 (*c* =1.5, $CHCl_3$)}.

3b (from L-Ser)

$[\alpha]_D^{25}$ −55.5 (*c* =1.0, $CHCl_3$) (from L-Ser).

(4*S*) and (4*R*)-4-(1-Hydroxy-1-methyethyl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidines (4a and 4b)

To a stirred suspension of Grignard reagent [prepared from Mg (5.6 g, 230.0 mmol) and MeI (16.8 mL, 270 mmol) in Et_2O (200 mL)] was added dropwise a solution of **3** (10.0 g, 38.6 mmol) in Et_2O (30 mL) at 0 °C. After stirring for 30 min at 0 °C, to the resulting solution was added dropwise an aq sat. NH_4Cl (100 mL). The mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (2 × 50 mL) and dried (Na_2SO_4). Concentration in vacuo gave a residue, which was purified on a silica gel column using a mixture of hexane and EtOAc (3:1, v/v) to give **4** as colorless crystals, which were recrystallized from a mixture of EtOAc and hexane to give **4** as colorless needles; yield: 10.3 g (quant.); mp 36−37 °C; $[\alpha]_D^{25}$ +23.0 (*c* =1.0, MeOH).

IR (KBr): ν = 3412, 2974, 2938, 2880, 1698, 1668 cm^{-1}.

^1H NMR (($CDCl_3$/TMS): δ = 1.18 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.51[(s, 12 H, $Boc(CH_3)_3$, $Ip(CH_3)$], 1.60 [s, 3 H, $Ip(CH_3)$], 3.78 (m, 1 H, 5-H), 4.00 (m, 2 H, 4-H), 5.30 (br s, 1 H, OH).

Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.32; H, 10.04; N, 5.21. Found: C, 60.21; H, 9.73; N, 5.40.

4b (from L-Ser)

mp 36−37 °C; $[\alpha]_D^{25}$ −22.5 (*c* =1.0, MeOH).

(4*S*) and (4*R*)-4-(1-Methylethenyl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidines (5a and 5b)

To a stirred solution of **4** (1.96 g, 7.33 mmol) in CH_2Cl_2 (20 mL) were added MsCl (2.8 mL, 36.6 mmol) and Et_3N (10.3 mL, 73.2 mmol) at −10 °C. After stirring at r.t. for 1 h, the mixture was poured into Et_2O (100 mL) and H_2O (60 mL). The organic layer was washed with aq 1 M 10% citric acid (3 × 50 mL), aq sat. $NaHCO_3$ solution (3 × 50 mL), brine (3 × 50 mL), and then dried (Na_2SO_4). Concentration in vacuo gave a residue, which was purified on a silica gel column using a mixture of hexane and EtOAc (8:1, v/v) to give **5** as a colorless syrup; yield: 1.35 g (76%); $[\alpha]_D^{25}$ +16.8 (*c* =1.2, MeOH).

IR (KBr): ν = 2980, 2932, 2872, 1704, 1660 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.41 [s, 3 H, $Ip(CH_3)$], 1.51 [s, 9 H, $Boc(CH_3)_3$], 1.66 [s, 3 H, $Ip(CH_3)$], 1.73 (s, 3 H, CH_3), 3.74 (dd, 1 H, *J* = 5.9, 8.8 Hz, 5-Ha), 4.07 (dd, 1 H, *J* = 7.3, 8.8 Hz, 5-Hb), 4.33 (dd, 1 H, *J* = 5.9, 7.3 Hz, 4-H), 4.85 (br s, 1 H, vinyl-Ha), 4.90 (br s, 1 H, vinyl-Hb).

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.43; H, 9.41; N, 5.55.

5b (from L-Ser)

$[\alpha]_D^{25}$ −15.5 (*c* =1.2, MeOH).

(2*S*)-2-(*N*-*tert*-Butoxycarbonyl)amino-3-methylbut-3-enol (6a)

A solution of **5a** (570mg, 2.36 mmol) in 70% AcOH (4 mL) was stirred at r.t. for 24 h. The mixture was concentrated in vacuo to give a residue, which was purified on a silica gel column using a mixture of hexane and EtOAc (5:1−2:1, v/v) to give **6a** as colorless crystals; yield: 157 mg (33%); mp 54−55 °C; $[\alpha]_D^{25}$ −10.5 (*c* = 1.0, MeOH).

IR (KBr): ν = 3376, 2980, 2938, 2878, 1692, 1653, 1524 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.45 [s, 9 H, Boc(CH_3)$_3$], 1.79 (s, 3 H, CH_3), 2.52 (br s, 1 H, OH), 3.68 (m, 2 H, 1-H), 4.10 (m, 1 H, 2-H), 4.97 (s, 1 H, vinyl-Ha), 5.00 (s, 1 H, vinyl-Hb), 5.12 (br s, 1 H, NH).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.45; H, 9.46; N, 6.73.

(2*S*) and (2*R*)-2-(*N*-*tert*-Butoxycarbonyl)amino-3-methylbut-3-enoic Acids (7a and 7b)

To a stirred solution of **5** (1.28 g, 5.23 mmol) in acetone (13 mL) was added Jones' reagent (4.0 ml, 10.7 mmol) at 0 °C. After stirring at r.t. for 12 h, Celite (1.0 g) and isopropyl alcohol (5.0 mL) were added to the mixture. The precipitate deposited was filtered off and the filtrate was adjusted to pH 9 with aq $NaHCO_3$ solution and then concentrated in vacuo. The aqueous layer was washed with Et_2O (2 × 20 mL) and acidified to pH 3 with citric acid. The resulting solution was extracted with EtOAc (3 × 20 mL) and the combined extracts were washed with brine (2 × 30 mL), and then dried (Na_2SO_4). Concentration in vacuo gave colorless crystals. Recrystallization from hexane gave **7** as colorless needles; yield: 843 mg (74%).

(2*S*)-**7a**

mp 60−66 °C; $[\alpha]_D^{25}$ +56.2 (*c* = 1.0, MeOH).

IR (KBr): ν = 3448, 2980, 1715, 1704, 1660, 1503 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.43 [s, H, Boc(CH_3)$_3$], 1.82 (s, 3 H, CH_3), 4.59, 4.80 (2 br s, 1 H, 2-H), 5.04 (br s, 1 H, vinyl-Ha), 5.12 (br s, 1 H, vinyl-Ha), 5.31, 7.38 (2 br s, 1 H, NH), 8.20 (br s, 1 H, CO_2H).

^{1}H NMR ($CDCl_3$/TMS, 65°C): δ = 1.44 [s, H, Boc(CH_3)$_3$], 1.82 (s, 3 H, CH_3), 4.72 (d, 1 H, *J* = 7.0 Hz, 2-H), 5.07 (d, 1 H, *J* = 5.5 Hz, vinyl-Ha), 5.08 (d, 1 H, *J* = 5.5 Hz, vinyl-Hb), 5.57 (br d, 1 H, *J* = 7.0 Hz, NH), 7.40 (br s, 1 H, CO_2H).

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.75; H, 8.20; N, 6.27.

(2*R*)-**7b** (from L-Ser)

mp 60−66 °C; $[\alpha]_D^{25}$ −56.2 (*c* = 1.0, MeOH).

(2*S*) and (2*R*)-2-Amino-3-methylbut-3-enoic Acid Hydrochlorides (8a and 8b)

To a stirred solution of **7** (110 mg, 0.51 mmol) in EtOH (500 μL) was added 3 M HCl (200 μL) at 0 °C. After stirring at r.t. for 30 min, the solution was concentrated and the residue dried in vacuo at 60°C to give a solid. Recrystallization from a mixture of EtOH and Et_2O to gave **8** as colorless needles; yield: 73 mg (92%).

(2*S*)-**8a**

mp 203−206 °C (dec.); $[\alpha]_D^{26}$ +114.5 (*c* = 1.0, H_2O). {Lit.[15] mp 201−204°C (dec.); $[\alpha]_D$ +113 (*c* = 3.64, H_2O)}.

IR (KBr): ν = 3432, 1636, 1508, 1404, 1338, 1261 cm^{-1}.

^{1}H NMR (D_2O, 25°C): δ = 1.68 (s, 3 H, CH_3), 4.18 (s, 1 H, 2-H), 5.99 (s, 1 H, vinyl-Ha), 5.13 (s, 1 H, vinyl-Hb),

Anal. Calcd for $C_5H_{10}NO_2Cl$: C, 39.57; H, 6.60; N, 9.23; Found: C, 39.75; H, 6.32; N, 9.05.

(2*R*)-**8b** (from L-Ser)

mp 202−205 °C (dec.); $[\alpha]_D^{26}$ −113.6 (*c* = 1.0, H_2O). {Lit.[15] mp 202−205 °C (dec.); $[\alpha]_D^{27}$ −112 (*c* = 3.44, H_2O)}.

(2*S*) and (2*R*)-2-(*N*-*tert*-Butoxycarbonyl)amino-3-hydroxy-3-methylbutanoic Acids (10a and 10b)

To a stirred solution of **4a** (3.3 g, 13.0 mmol) in acetone (100 mL) was added Jones' reagent (7.3 mL, 19.5 mmol) at 0 °C. After stirring for 1.5 h, Celite (2 g) and isopropyl alcohol (30 mL) were added to the mixture. The precipitate deposited was filtered off and the filtrate was adjusted to pH 8 with aq $NaHCO_3$ solution and then concentrated in vacuo. The aqueous layer was washed with Et_2O (2 × 50 mL) and acidified to pH 3 with citric acid. The resulting solution was extracted with EtOAc (3 × 50 mL) and the combined extracts were washed with brine (2 × 50 mL), and then dried (Na_2SO_4). Concentration in vacuo gave colorless crystals. Recrystallization from a mixture of hexane and EtOAc gave **10** as colorless needles; yield: 1.85 g (66%); mp 164−165.5 °C; $[\alpha]_D^{29}$ −7.0 (*c* = 1.0, MeOH).

IR (KBr): ν = 3304, 2968, 2110, 1587 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.18 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 3.97 (d, 1 H, *J* = 8.8 Hz, 2-H), 5.05 (s, 2 H, Cbz's CH_2), 7.17 (br d, 1 H, *J* = 8.8 Hz , NH), 7.36 (s, 5 H, C_6H_5), 12.50 (br s, 1 H, CO_2H).

Anal. Calcd for $C_{13}H_{17}NO_5$.0.5 H_2O: C, 56.51; H, 6.20; N, 5.07. Found: C, 56.47; H, 5.88; N, 4.64.

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