SYNTHESIS OF OPTICALLY PURE β-PHENYLSELENOALANINE THROUGH SERINE-β-LACTONE : A USEFUL PRECURSOR OF DEHYDROALANINE†

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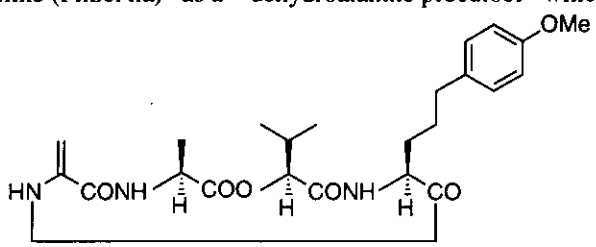
Abstract - Optically pure L- and D-β-phenylselenoalanines (PhSeAla), useful precursors of dehydroalanine, were synthesized from L- and D-serine-β-lactone. Elimination reactions of the phenylseleno group to form the dehydroalanine were examined.

Dehydroamino acids are fundamental constituents in various antibiotics, antitumor and phytotoxic peptides, and the introduction of dehydroamino acids into a peptide usually changes its conformation and biological activity.[1] Recently, we synthesized a host-specific phytotoxin, alternariolide (AM-toxin I),[2] a cyclic tetradepsipeptide containing dehydroalanine. During the synthesis, cyclization and the dehydroalanine formation were crucial steps whose success was deeply dependent on the stereochemistry[3] of the dehydroalanine precursor and the mode of elimination reaction, such as syn or anti. We used optically pure D-β-phenylselenoalanine (PhSeAla)[4] as a dehydroalanine precursor[5] which should be a satisfactory

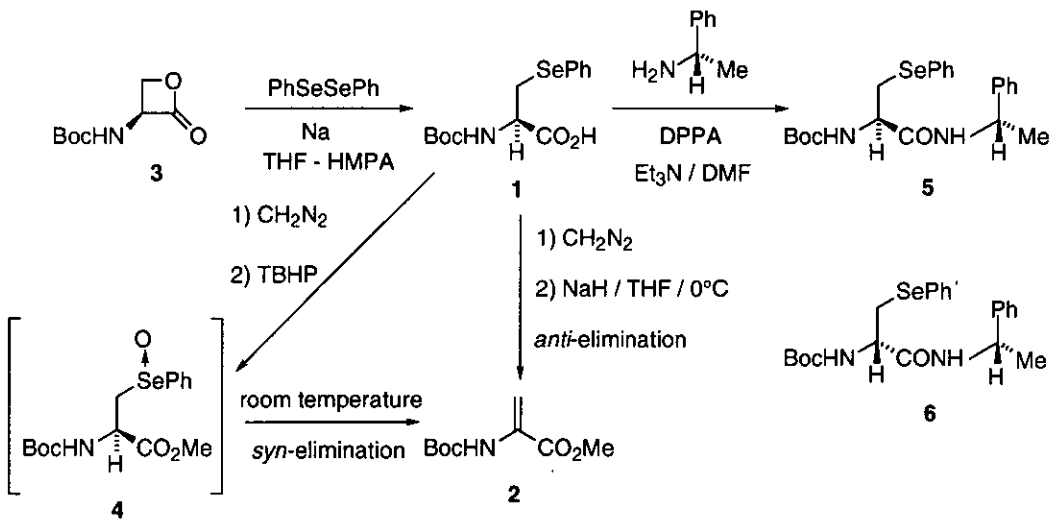


Alternariolide (AM-toxin I)

† Dedicated to Dr. Shigeru Oae, Professor Emeritus Tsukuba University in celebration of his 77th birthday.

precursor of dehydroalanine, since the phenylseleno group is allowed to proceed by elimination through both the syn and anti modes depending on the reaction conditions.[6] A synthetic method for L-PhSeAla has already been reported using an enzyme by the substitution reaction of L-cystein and other amino acids with phenylselenol,[7] but the D-form was not available. We synthesized both enantiomers of N-Boc-PhSeAla in optically pure forms through Vederas' serine-β-lactone.[8]

L-Serine-β-lactone (**3**) prepared according to Vederas' procedure was reacted with sodium phenylselenide[9] prepared from diphenyl diselenide with sodium in THF-HMPA to give N-Boc-L-PhSeAla (**1**) in 93% yield. In this reaction, the serine derivative was not observed which would be produced by attack of the phenylselenide anion on the carbonyl group. The optical purity of **1** was checked after conversion to **5** by comparing the ^{1}Hnmr spectrum of **5** with that of **6**, which was separately prepared from the corresponding D-β-lactone (**ent-3**) and showed that a detectable amount of **6** was not produced in the reaction.



The elimination reactions of the phenylseleno group of **1** were examined. After conversion of **1** to its methyl ester, the ester was exposed to NaH in THF at 0℃ to give desired dehydroalanine (**2**)[10] in 98% yield. The phenylseleno group easily reacted *via* elimination under basic conditions, but is enough stable under weakly basic conditions which are usually used in the peptide formation reactions.

On the other hand, the corresponding selenoxide (**4**) smoothly underwent elimination at room temperature under neutral conditions to afford **2** in 93% yield. For the oxidation of selenide to selenoxide, O_3, mCPBA,

H_2O_2aq, TBHP were effective, of these, anhydrous TBHP would be the best choice.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured using a JASCO DIP-370 digital polarimeter. Ir spectra were recorded using a JASCO FT / IR-8000 spectrophotometer. ^{1}HNmr spectra were recorded using a JEOL α-400 spectrometers. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz. High resolution mass (HRms) were obtained using a JEOL Model JMS-D300 instrument.

N-Boc-L-β-phenylselenoalanine (**1**)

To a solution of diphenyldiselenide (1.06 g, 0.6 equiv.) in THF (8.5 ml) was added pieces of Na (181 mg, 1.4 equiv.) and the resulting mixture was refluxed for 5 h under argon. To the resulting solution were dropwise added HMPA (0.08 ml, 0.1 equiv.) and L-Serine-β-lactone (**3**, 1.06 g, 5.7 mmol) in THF (12.0 ml) at 0℃ and the mixture was stirred for 5 min. After addition of MeOH to the mixture for decomposition of excess Na, the solution was concentrated in vacuo. The residue was dissolved in aqueous saturated $NaHCO_3$ and the mixture was washed with Et_2O (15 ml x 3). The aqueous phase was adjusted to pH 2 with 1N HCl and extracted with AcOEt (15 ml x 3). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solution was evaporated in vacuo and the residue was crystallized from AcOEt-hexane to give **1** (1.8 g, 93%) as colorless needles. mp 91-92℃; $[\alpha]_D$ -38.1° (c 1.00, MeOH) ; ^{1}Hnmr (400 MHz, $CDCl_3$, TMS) δ 1.42(9H, s), 3.35(2H,m), 4.39(1H, br s), 4.63(1H, m), 5.29(1H, d, J=7.3), 7.26(3H, m), 7.56(2H, m); ir (cm^{-1}, nujol) 3312, 2924, 2855, 1734, 1655, 1414, 1244, 1221; EI-HRms 345.0480 (M^+) calcd for $C_{14}H_{19}O_4N^{80}Se$, 345.0480.

N-Boc-D-β-phenylselenoalanine (**ent-1**)

To a solution of diphenyl diselenide (1.5 g, 0.6 equiv.) in THF (12.0 ml) was added pieces of Na (258 mg, 1.4 equiv.) and the resulting mixture was refluxed for 4 h under argon. To the resulting solution were dropwise added HMPA (0.11 ml, 0.1 equiv.) and D-Serine-β-lactone (**ent-3**, 1.5 g, 8.0 mmol) in THF (16.0 ml) at 0℃ and the mixture was stirred for 5 min. After addition of MeOH to the mixture for decomposition of excess Na, the solution was concentrated in vacuo. The residue was dissolved in

aqueous saturated $NaHCO_3$ and the mixture was washed with Et_2O (15 ml x 3). The aqueous phase was adjusted to pH 2 with 1N HCl and extracted with AcOEt (20 ml x 3). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solution was evaporated in vacuo and the residue was crystallized from AcOEt-hexane to give **ent-1** (2.56 g, 93%) as colorless needles. mp 90-91℃; $[\alpha]_D$ +39.5°(c 1.00, MeOH).

N-Boc-L-β-phenyselenoalanine (S)-(-)-α-methylbenzylamide (**5**)

To a solution of (S)-(-)-α-methylbenzylamine (17 mg) in DMF (1.0 ml) were added L-β-phenylselenoalanine (48 mg, 1.0 equiv) , DPPA (0.03 ml, 1.1 equiv), and Et_3N (0.02 ml, 1.1 equiv) and the mixture was stirred for 2 h at 0℃ and then over night at room temperature. The mixture was poured into water and extracted with AcOEt (1 ml x 3). The combined extract was washed with brine, dried over anhydrous Na_2SO_4. After filtration the solution was evaporated in vacuo and the resulting mixture was purified on silica gel to give **5** (48 mg, 77%) as colorless needles. mp 134℃; $[\alpha]_D$ -38.4° (c 0.27, $CHCl_3$) ; ^{1}Hnmr (400 MHz, $CDCl_3$, TMS) δ 1.41(9H, s), 1.46(3H, d, J=7.1), 3.17(1H, m), 3.33(1H, dd, J=6.2, 12.8), 4.26(1H, br s), 5.05(1H, m), 5.24(1H, br s), 6.48(1H, d, J=6.6), 7.28(8H, m), 7.49(2H, m); ir (cm^{-1}, nujol) 3326, 2924, 2855, 1686, 1651, 1273, 1163; EI-HRms m/z 448.1265 (M^+) calcd for $C_{22}H_{28}O_3N_2{}^{80}Se$, 448.1265.

N-Boc-D-β-phenyselenoalanine (S)-(-)-α-methylbenzylamide (**6**)

To a solution of (S)-(-)-α-methylbenzylamine (24 mg, 1.0 equiv.) in DMF (1.0 ml) were added D-β-phenyselenoalanine (67 mg) , DPPA (0.05 ml, 1.1 equiv), and Et_3N (0.03 ml, 1.1 equiv) and the mixture was stirred for 2 h at 0℃ and then over night at room temperature. The mixture was poured into water and extracted with AcOEt (1 ml x 3). The combined extract was washed with brine, dried over anhydrous Na_2SO_4. After filtration the solution was evaporated in vacuo and the resulting mixture was purified on silica gel to give **6** (64 mg, 73%) as a colorless oil. : $[\alpha]_D$ +20.9° (c 0.30, $CHCl_3$) ; ^{1}Hnmr (400 MHz, $CDCl_3$, TMS) δ 1.40(9H, s), 1.45(3H, d, J=7.1), 3.21(1H, dd, J=6.7, 12.6), 3.30(1H, dd, J=6.7, 12.6), 4.30(1H, br s), 5.05(1H, quintet, J=7.1), 5.19(1H, br s), 6.35(1H, br s), 7.29(8H, m), 7.53(2H, m); ir (cm^{-1}, neat) 3266, 3073, 2976, 1686, 1651, 1557, 1514, 1248, 1169, 1024; EI-HRms m/z 448.1266 (M^+)

calcd for $C_{22}H_{28}O_3N_2{}^{80}Se$, 448.1265.

N-Boc-dehydroalanine methyl ester (**2**)

Basic conditions (anti-elimination)

To a suspension of 100% NaH (5 mg, 1.4 equiv.) in THF (0.3 ml) was slowly added **1** (58 mg) in THF (0.7 ml) at 0℃ and the resulting mixture was stirred for 3 min. The mixture was poured into water and extracted with AcOEt (1 ml x 3). The combined extract was washed with brine, dried over anhydrous Na_2SO_4. After filtration the solution was evaporated in vacuo. The residue was chromatographed on silica gel to give **2** (16 mg, 98%) as a colorless oil. ^{1}HNmr (400MHz, $CDCl_3$, TMS) δ 1.49(9H, s), 3.83(3H, s), 5.73(1H, m), 6.17(1H, s), 7.02(1H, br s).

Neutral conditions (syn-elimination)

To a solution of **1** (64 mg) in CH_2Cl_2 (1.0 ml) was added 4.03 M TBHP in CH_2Cl_2 (0.22 ml, 5.0 equiv.) at 0℃ and the mixture was stirred for 2 h at room temperature. The mixture was concentrated *in vacuo* and the residue was extracted with Et_2O. The combined extract was washed with brine, dried over anhydrous Na_2SO_4. After filtration the solution was evaporated *in vacuo* and the residue was chromatographed on silica gel to give **2** (17 mg, 93%) as a colorless oil.

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