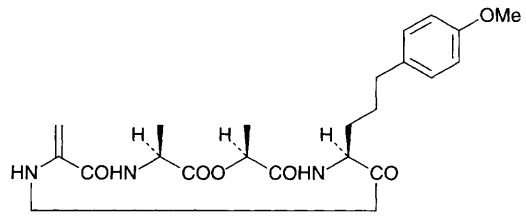
β-Phenylselenoalanine as a dehydroalanine precursor–efficient synthesis of alternariolide (AM-toxin I)

Kimiko Hashimoto,[a] Mitsuru Sakai,[a] Toshikatsu Okuno[b] and Haruhisa Shirahama*[a]

[a] *School of Science, Kwansei Gakuin University, Uegahara, Nishinomiya 662, Japan*
[b] *Faculty of Agriculture, Hirosaki University, Hirosaki 036, Japan*

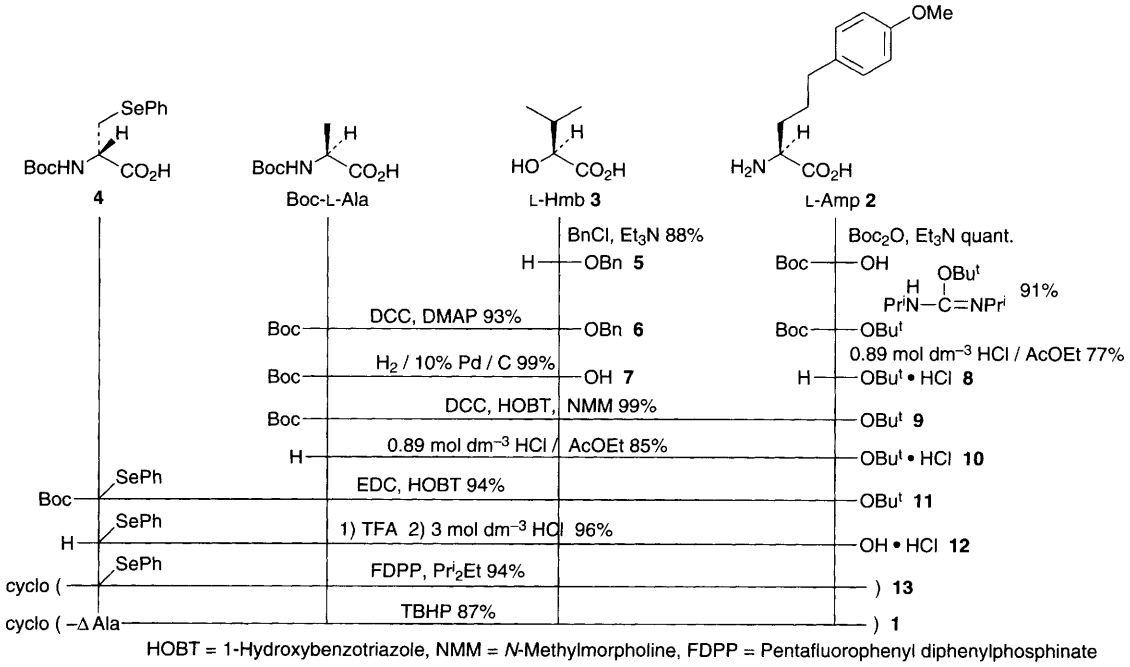
Alternariolide (AM-toxin) is synthesized in 44% overall yield from L-2-amino-5-(4-methoxyphenyl)pentanoic acid; D-β-phenylselenoalanine is used as the dehydroalanine precursor.

Alternariolide (AM-toxin I)[1] **1** produced by *Alternaria mali* has been found to be responsible for the necrotic brown spots on certain apple leaves, which is the first example of a host specific phytotoxin.[2] Alternariolide is a cyclic tetradepsipeptide containing two unusual amino acids, dehydroalanine (Δ-Ala) and L-2-amino-5-(4-methoxyphenyl)pentanoic acid (L-Amp) **2**, and L-2-hydroxy-3-methylbutylic acid (L-Hmb) **3**. Some syntheses of this peptide[3] and its analogues[4] have met with difficulties during the cyclization step and dehydroalanine formation, resulting in unsatisfactory yields. We describe here an efficient synthesis of **1** using FDPP (pentafluorophenyl diphenylphosphinate)[5] for the cyclization and β-phenylselenoalanine **4** for the dehydroalanine formation.



Alternariolide (AM-toxin I) **1**

L-Hmb **3** was prepared according to Ourisson's procedure.[6] L-Amp **2** was synthesized from 4-methoxyphenylpropionic acid by the following sequence of reactions: (i) reduction with $LiAlH_4$; (ii) bromination with PBr_3; (iii) condensation with diethyl acetoamidomalonate using NaOEt in EtOH; (iv) hydrolysis of the esters with 2 mol dm^{-3} NaOH followed by decarboxylation in acidic conditions; and (v) deacetylation of the L-form with an acylase (*Aspergillus genus*). D-β-Phenylselenoalanine **4** was synthesized from (*R*)-*N*-Boc-serine-β-lactone[7] using PhSeNa (prepared from PhSeSePh with Na[8]) in THF–HMPA without racemization. The obtained amino and α-hydroxy acids were then condensed in the following sequence: Boc-L-Ala was condensed with L-Hmb-OBn **5** using DCC and DMAP. After hydrogenolysis of the benzyl ester **6**, the resulting carboxylic acid **7** was coupled with L-Amp-OBu^t·HCl **8** (prepared from L-Amp with (i) Boc_2O and Et_3N, (ii) *O-tert*-butyldiisopropylisourea[9] and (iii) 0.89 mol dm^{-3} HCl–AcOEt[10]) to give the tridepsipeptide **9**. Removal of the Boc group of **9** followed by condensation with D-β-phenylselenoalanine **4** gave the linear tetradepsipeptide **11**. For the cyclization reaction, the protective groups of both ends in **11** were sequentially removed and the resulting salt **12** was treated with FDPP in the presence of Pr^i_2NEt in 4 mmol dm^{-3} DMF at room temperature to give the desired cyclodepsipeptide in 94% yield. As previously reported by Izumiya's group,[11] the use of the D-amino acid as the dehydroalanine precursor was also effective in the cyclization step. When the corresponding L-β-



HOBT = 1-Hydroxybenzotriazole, NMM = *N*-Methylmorpholine, FDPP = Pentafluorophenyl diphenylphosphinate

phenylselenoalanine was used in place of the D-**4**, the cyclization reaction failed. In the final dehydroalanine formation step, all synthetic efforts towards **1** have so far utilized an *anti*-elimination reaction, *e.g.* sulfonate elimination, and Hofmann eliminations which need vigorous conditions thus resulting in a poor yield. The phenylselenoxide group undergoes a *syn*-elimination under mild conditions. Thus, the synthesis of alternariolide was performed by oxidation–elimination of the phenylselenyl group using anhydrous *tert*-butylhydroperoxide (TBHP) in CH_2Cl_2–TFE[12] (5 : 1) at room temperature overnight to give **1** in 87% yield. The synthetic **1** was identical to a natural sample from both spectral and biological aspects.

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