

# $\beta$ -Phenylselenoalanine as a dehydroalanine precursor—efficient synthesis of alternariolide (AM-toxin I)

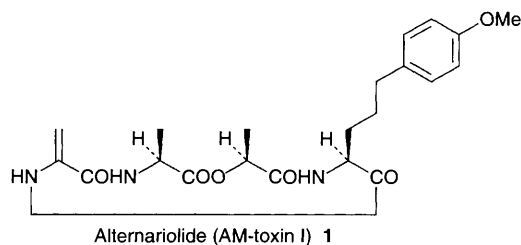
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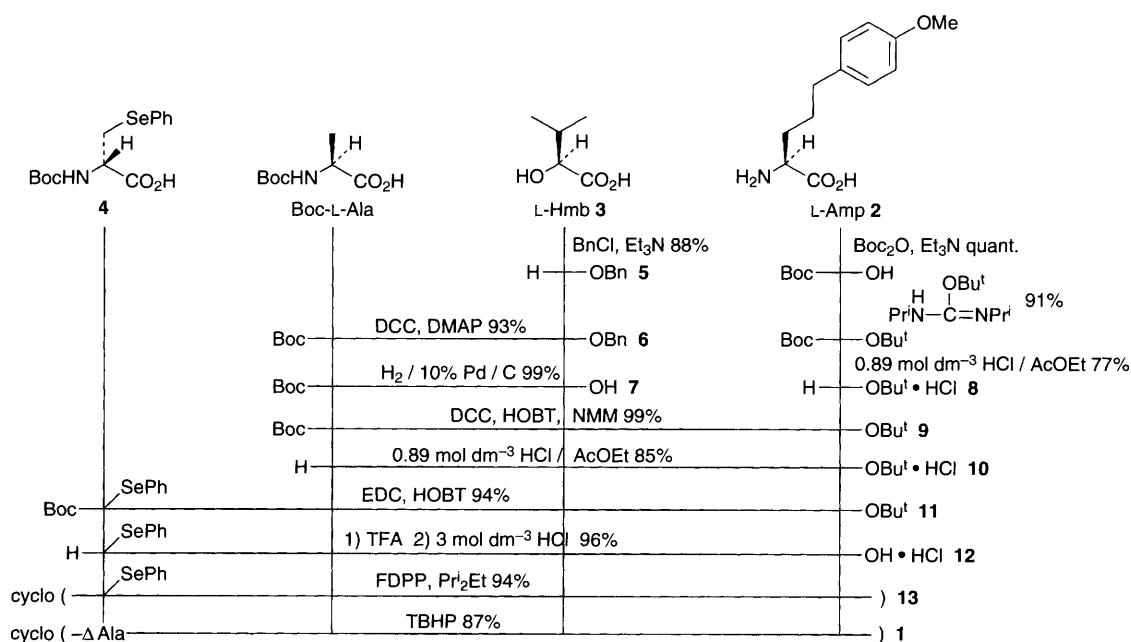
Alternariolide (AM-toxin I) is synthesized in 44% overall yield from L-2-amino-5-(4-methoxyphenyl)pentanoic acid; D- $\beta$ -phenylselenoalanine is used as the dehydroalanine precursor.

Alternariolide (AM-toxin I)<sup>1</sup> 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.<sup>2</sup> Alternariolide is a cyclic tetradepsipeptide containing two unusual amino acids, dehydroalanine ( $\Delta$ -Ala) and L-2-amino-5-(4-methoxyphenyl)pentanoic acid (L-Amp) **2**, and L-2-hydroxy-3-methylbutyric acid (L-Hmb) **3**. Some syntheses of this peptide<sup>3</sup> and its analogues<sup>4</sup> 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 diphenylphos-



phinate)<sup>5</sup> for the cyclization and  $\beta$ -phenylselenoalanine **4** for the dehydroalanine formation.

L-Hmb **3** was prepared according to Ourisson's procedure.<sup>6</sup> L-Amp **2** was synthesized from 4-methoxyphenylpropionic acid by the following sequence of reactions: (i) reduction with LiAlH<sub>4</sub>; (ii) bromination with PBr<sub>3</sub>; (iii) condensation with diethyl acetoamidomalonate using NaOEt in EtOH; (iv) hydrolysis of the esters with 2 mol dm<sup>-3</sup> NaOH followed by decarboxylation in acidic conditions; and (v) deacetylation of the L-form with an acylase (*Aspergillus* genus). D- $\beta$ -Phenylselenoalanine **4** was synthesized from (*R*)-*N*-Boc-serine- $\beta$ -lactone<sup>7</sup> using PhSeNa (prepared from PhSeSePh with Na<sup>8</sup>) in THF-HMPA without racemization. The obtained amino and  $\alpha$ -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<sup>t</sup>·HCl **8** (prepared from L-Amp with (i) Boc<sub>2</sub>O and Et<sub>3</sub>N, (ii) *O*-tert-butyl diisopropylisourea<sup>9</sup> and (iii) 0.89 mol dm<sup>-3</sup> HCl·AcOEt<sup>10</sup>) to give the tridepsipeptide **9**. Removal of the Boc group of **9** followed by condensation with D- $\beta$ -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<sub>2</sub>NEt in 4 mmol dm<sup>-3</sup> DMF at room temperature to give the desired cyclodepsipeptide in 94% yield. As previously reported by Izumiya's group,<sup>11</sup> the use of the D-amino acid as the dehydroalanine precursor was also effective in the cyclization step. When the corresponding L- $\beta$ -



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<sub>2</sub>Cl<sub>2</sub>-TFE<sup>12</sup> (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.

## References

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