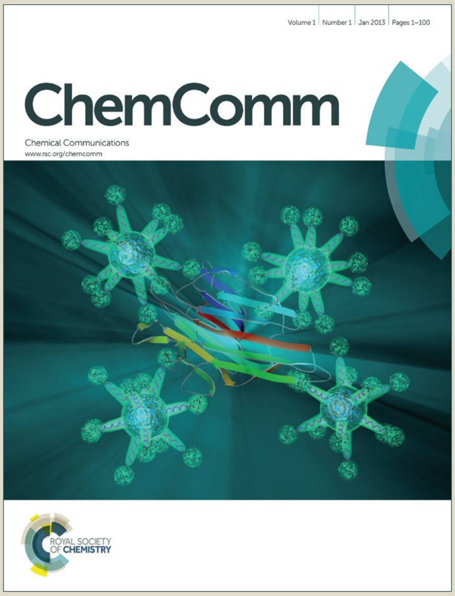
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A Stereoselecitve Construction of *E*- and *Z*-Δ-Ile from *E*-Dehydroamino Acid Ester: the Synthesis of Phomopsin A Tripeptide Side Chain

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Stereoselective synthesis of the phomopsine A tripeptide side chain was achieved by using methyl 2-(((benzyloxy)carbonyl)amino)-2-(diphenoxyphosphoryl)acetate as a common synthetic precorsor for the synthesis of *E*-Δ-dehydroisoleusine and *E*-Δ-aspartate.

Phomopsin A (**1**) was isolated from the fungus species *Diaporthe toxica* as the main mycotoxin of lupinosis (Fig. 1).[1] Phomopsin A (**1**) and its natural congener, phomopsin B (**2**), are potent inhibitors of microtubule depolymerization at <1 μM.[2] Phomopsin A (**1**) and B (**2**) are consisted of four dehydroamino acids (Dhaas) and two highly oxidized unusual amino acids. Their characteristic structures and potent pharmacological activities have attracted much attention as a synthetic target.[3-5] The first total synthesis of phomopsin B (**2**) was achieved by Wandless *et al*.[3] Joullié *et al*. reported the synthesis of the tripeptide side chain.[5] The total synthesis of the structurally more complex phomopsin A (**1**) has not been reported yet.

The stereoselective synthesis of the tripeptide side chain is one of the challenging synthetic tasks in view of their stereo control and linkage. Previously, the synthesis was accomplished by the stereoselective dehydration of β-hydroxyisoleucine **4** and β-hydroxyaspartate **5** as surrogates for the *E*-Δ-Ile and *E*-Δ-Asp moieties, respectively (Fig. 2).[5,6] In the precedent route, the geometrical control depends on the reaction mode of the β-elimination and the stereochemistry of **4** and **5**. To elaborate the requisite stereochemistry, **4** and **5** were selectively prepared in several steps. Herein, we would like to report a new synthetic route to access the tripeptide side chain. Our approach is characterized by simplifying the synthetic route with α-(diphenylphosphono)glycine **3** as a common synthetic precursor and the stereocontrolled construction of the *E*-Δ-Ile and *E*-Δ-Asp moieties on the peptide side chain under the mild conditions.

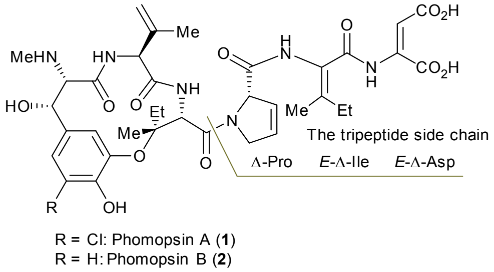

Fig. 1 Structures of phomopsin A and B.

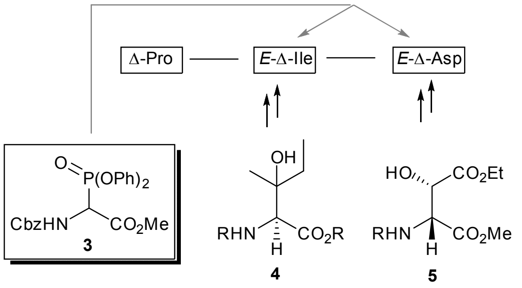

Fig. 2 Structures of α,β-unsaturated amino acid precursors.

Our strategy is outlined in Scheme 1. In consideration of the instability of the NH_2-free dehydroamino acid ester,[7] **3** was sequentially introduced from the *C*-terminal of **6** and **8**. Conversion of **7** to **8** involves the construction of the *E*-Δ-Ile[8–12] moiety. To this challenging task, we tackled an unprecedented approach by a series of sequential transformations: i) *E*-selective olefination of **7**, ii) *Z*-selective iodination of the resulting *E*-dehydroamino acid, and iii) the Negishi-cross coupling reaction. It was anticipated that the remaining *E*-Δ-Asp moiety would be stereoselectively prepared from **9** by our original synthetic method to access *E*-dehydroamino acid esters using **3**.[13]

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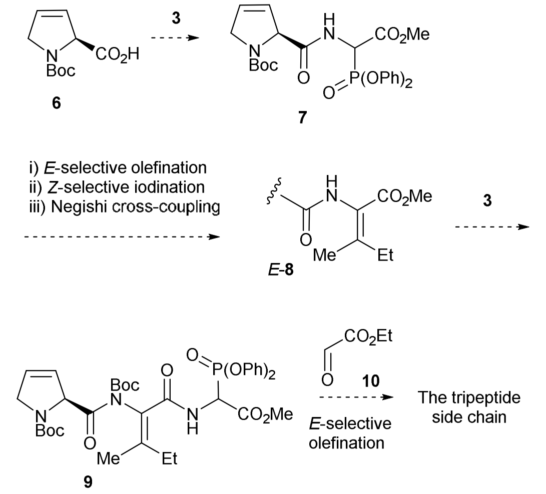
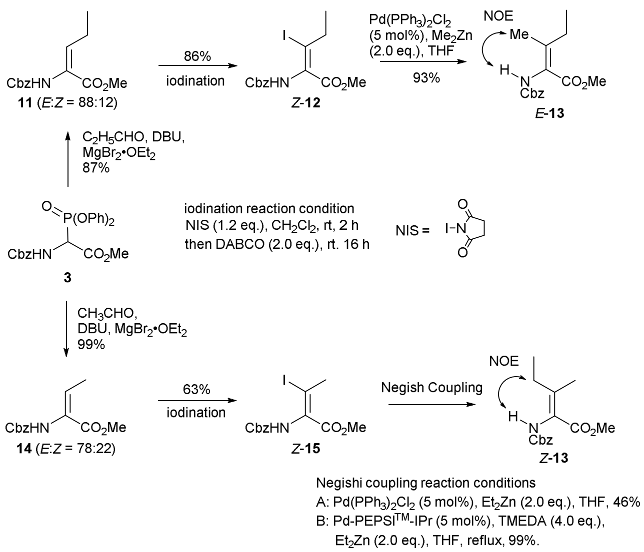


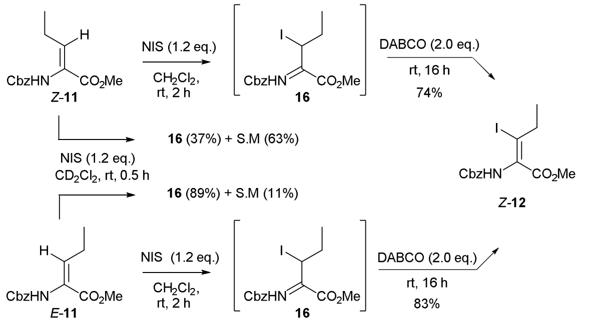
Scheme 1 Synthetic plan.

A model study for the synthesis of *E*-**8** from **7** was examined by the synthesis of *E*- and *Z*-Δ-Ile **13** from **3** (Scheme 2). The *E*-selective Horner–Wadsworth–Emmonds reaction of **3**[13] with propanal in the presence of DBU and $MgBr_2$•OEt_2 gave *E*-**11** [*E:Z* = 88:12] in 87% yield. Treatment of **11** with NIS and DABCO[14] provided the thermodynamically stable *Z*-iodide **12** as a single isomer in 86% yield. The Negishi cross-coupling reaction of *Z*-**12** with Me_2Zn in the presence of 5 mol% of $Pd(PPh_3)_2Cl_2$ in THF at room temperature proceeded smoothly to give *E*-**13** as a sole product in 93% yield. The stereochemistry of *E*-**13** was confirmed by NOESY analysis and comparison with its authentic ^{13}C-NMR data.[8] It is noteworthy that the NHCbz, methoxycarbonyl group, and N-acyl enamine moieties were tolerated under the mild conditions. The synthetic utility was successfully displayed in the synthesis of *Z*-**13** from **3**. The *E*-selective olefination of **3** and acetaldehyde provided *E*-**14** [*E:Z* = 78:22, 99% yield],[13] followed by the iodination reaction to give *Z*-**15** in 63% yield. In contrast to the facile cross-coupling of *Z*-**12** with Me_2Zn in the Negishi reaction, that of *Z*-**15** with Et_2Zn resulted in moderate yield (46%). We supposed that undesired side reactions such as the competitive β-H elimination from an Et-Pd species might decrease the catalytic ability. This was solved by switching the ligand to TMEDA which is known to be an effective ligand to supress the side reaction by saturation of the coordination sphere of the Pd catalyst.[15] Gratifyingly, the cross-coupling process was extremely improved by using TEMDA and a robust Pd catalyst, Pd-PEPSI^{TM}-IPr, to give *Z*-**13** in 99% yield. Stereochemistry of *Z*-Δ-Ile **13** was determined by NOESY experiments and comparison of its NMR data with those of *E*-Δ-Ile **13**.[8]



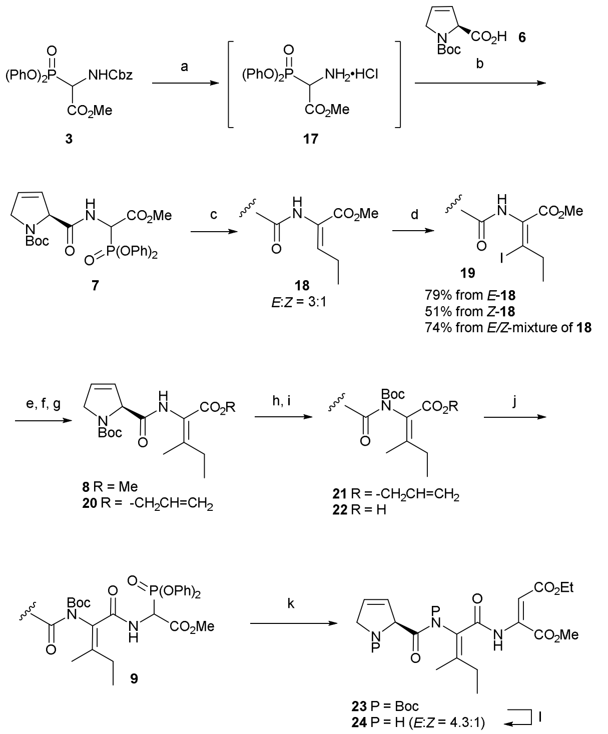
Scheme 2 Synthesis of *E*-Δ-Ile **13** and *Z*-Δ-Ile**13**.

The above new method is characterized by the mild reaction conditions and the use of *E*-**11** as a superior substrate to *Z*-**11** for the initial iodination reaction. The use of *E*-**11** in the iodination reaction is quite rare. Supports for the synthetic advantage of *E*-Dhaas in the iodination reaction came from the following comparative experiments of *E*-**11** and *Z*-**11** (Scheme 3). Treatment of *Z*-**11** with NIS gave a new spot on TLC which was supposed to be the imine intermediate **16**.[16] The starting material was consumed after 2 h. Without isolation of **16**, the crude imine was subjected to the base-promoted isomerization reaction with DABCO to provide *Z*-**12** in 74% yield. Under the conditions, no starting material was recovered. It was conceivable that undesired side reactions might compete during the course of the imine formation. To accelerate the rate of the imine formation, we turned our attention to *E*-**11**. It is anticipated that *E*-**11** would be more reactive than *Z*-**11** because of its higher torsional strain caused by the steric repulsion between the ethyl and methoxycarbonyl groups. To assess the reactivity of *E*-**11** with NIS, iodination reactions of *E*-**11** and *Z*-**11** were conducted in CD_2Cl_2. The conversion ratios were analysed by ^{1}H-NMR. We found that the conversion of *E*-**11** to the imine intermediate **16**[16] was superior to that of *Z*-**11** [conversion ratio after 0.5 h: 89% vs 37%]. Moreover, treatment of *E*-**11** with NIS for 2h followed by the DABCO-promoted isomerization gave *Z*-**12** in 83% yields. These results indicated that the potential synthetic utility of *E*-Dhaas for the advanced iodination substrate. The synthetic advantage was proved by the synthesis of the tripeptide side chain shown in Scheme 4.



Scheme 3 Comparative experiments of *E*-**11** and *Z*-**11**.

The synthesis of the tripeptide side chain was commenced with the coupling reaction of **17** with 3,4-Δ-Pro **6**. Removal of the Cbz group of **3** under the hydrogenation reaction condition gave ammonium salt **17**. Without isolation, **17** was linked with **6** to give **7** in 55% yield. The olefination reaction of **7** with propanal gave a 3:1 mixture of *E*-**18** and *Z*-**18** in 91% yield. After the separation, *E*-**18** and *Z*-**18** were separately subjected to the iodination reaction using NIS and DABCO. Iodide **19** was produced in 79 % yield from *E*-**18** and 51% yield from *Z*-**18.** These results revealed that *E*-**18** was superior to *Z*-**18** in the synthesis of **19**.[17] It is interesting to note that the iodination reaction occurred at the dehydroamino acid moieties without significant loss of the double bond in the Δ-Pro moiety due provably to the reactive enamine character of Dhaas. The Negishi coupling reaction of **19** with Me_2Zn in the presence of 3 mol% of Pd-PEPSI^{TM}-IPr provided **8** in 94% yield.



Scheme 4 Synthesis of the tripeptide side chain **24**. *Reagent and conditions*: a) H_2, Pd/C, HCl in MeOH, EtOAc; b) **6**, EDCI, DMAP, CH_2Cl_2,DMF, 55% over 2 steps; c) propanal, DBU, $MgBr_2 \cdot OEt_2$, THF, 91% (*E*:*Z* = 74:26); d) NIS, $CHCl_3$, 50 °C then DABCO, rt, 74% (*Z* only); e) Pd-PEPPSI^{TM}-IPr, Me_2Zn, THF, 94%. f) $LiOH \cdot H_2O$, THF/H_2O, 50 °C; g) allyl bromide, Cs_2CO_3, DMF, 86% over 2 steps; h) Boc_2O, DMAP, CH_2Cl_2, quant.; i) $Pd(PPh_3)_4$, morpholine, THF; j) **7**, EDCI, DMAP, CH_2Cl_2/DMF, 56% over 2 steps; k) **10**, DBU, $ZnCl_2$, THF, 80%, l) TFA, CH_2Cl_2 then Preparative TLC, 35%.

It has been reported that the peptide bond forming reaction at the carboxylic acid moiety of Δ-Ile requires the protection of the amide N-H to avoid the formation of the corresponding azlactone and its undesired olefin isomerization.[5,10] Accordingly, the N-H of the coupling precursor **21** was protected with a Boc group prior to the peptide coupling reaction. Methyl ester **8** was converted to allyl ester **20** in 86% yield in 2 steps. The N-H group of **20** was protected with a Boc group, followed by the removal of the allyl group to give the appropriately protected coupling precursor **22**. The peptide bond forming reaction of **22** with **17** provided **9** in 56% yield without any olefin isomerization. The synthesis of the phomopsin A tripeptide side chain *E*-**23** was furnished by the *E*-selective Dhaa forming reaction developed by us.[13] Phosphonate **9** was condensed with **10** in the presence of DBU/$ZnCl_2$ to afford *E*-**23** in 80% yield. Removal of the Boc groups of **23** with TFA provided a 4.3:1 mixture of *E*-**24** and *Z*-**24**. The mixture was purified by preparative TLC to give *E*-**24** in 35% yield with the inseparable *E/Z*-mixture (18% yield). The *E*-geometry of the resulting Δ-Asp moiety was confirmed by comparison of the chemical shift values of the olefinic protons (*E*: 6.05 ppm, *Z*: 5.46 ppm).[13]

In summary, we have developed a novel synthetic route to access the phomopsin A tripeptide side chain **24** in 12 steps from **3**. The synthesis could be simplified by the use of α-(diphenylphosphono)glycine **3** as a common surrogate of *E*-Δ-Ile and *E*-Δ-Asp moieties. The carbon-carbon bond forming reactions on the peptide chain was successfully achieved under the mild conditions. Total synthesis of phomopsin A and Δ-Ile-containing natural products[18] as well as studies from the view point of chemical biology[19] of Δ-Ile-containing biologically active molecules are in progress.

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