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A copper-carbodiimide approach to the phomopsin tripeptide side chain

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ABSTRACT

A one-step copper-carbodimide elimination was used to provide the (*E*)-dehydroisoleucine moiety in the phomopsin side chain stereoselectively. An efficient approach to the phomopsin tripeptide side chain was developed to be used in the total syntheses of phomopsins A and B.

Dehydroamino acids are important moieties in biological investigations and are found in many natural products including roquefortine C and E,[1] azinomycins A and B,[2]and AM-toxins and tentoxin.[3] Dehydroamino acids introduce conformational rigidity and change the reactivities of peptides. They are also important intermediates in the biosynthesis of other non-proteinogenic amino acids and D-amino acids.

Phomopsins A (**1**) and B (**2**) are natural products isolated from the fungus species *Phomopsis leptostromiformisa* and potent inhibitors of microtubule polymerization (Fig. 1).[4] A significant structural feature of phomopsins A and B is an unsaturated tripeptide side chain, which contains dehydroisoleucine and dehydroaspartate. This side chain was reported to be important for the molecular interaction of **1** with tubulin.[5] In this Letter, we describe an efficient and stereoselective synthesis of the phomopsin tripeptide side-chain precursor.

Synthesis of the phomopsin side chain requires a stereoselective method to prepare (*E*)-dehydroisoleucine. Many methods are available for the synthesis of dehydroamino acids, and elimination of water from β-hydroxy-α-amino acids is a well established route. Activation of the hydroxyl group for elimination can be achieved by many reagents: DAST/*N,N*-diisopropylethyl amine (DIPEA), tosyl chloride, mesyl chloride, Martin's sulfurane, and triphenyl phospine/diethyl azodicarboxylate (DEAD).[6] However, these methods are not highly stereoselective for *E/Z* isomers if there is no strong thermodynamic preference. Wandless and co-workers first reported an *anti*-selective two-step cyclic sulfamidate approach to the (*E*)-dehydroisoleucine. Based on this method they reported a total synthesis of phomopsin B in 2007.[7] Ferreira et al. also reported an *anti*-selective Boc anhydride/DMAP elimination method. Under their conditions all amides were Boc-protected.[8] In addition to elimination approaches, the Horner–Wadsworth–Emmons reaction has also been utilized to form the double bond.[9] The vinyl amidation method which couples amides and vinyl halides is another useful approach to synthesize dehydroamino acids.[10]

We now describe a one-step copper-carbodimide elimination that provides the required (*E*)-dehydroisoleucine in a highly stereoselective manner. The copper-carbodimide elimination method was first reported in 1960s.[11] Sai et al. found that this elimination method could give high *syn*-selective *E/Z* enamides.[12] The utility of the copper-carbodimide method to prepare dehydroamino acids in a natural product was demonstrated in the total synthesis of roquefortine C.[13]

N-Boc-dehydroproline (**5**) was prepared by a three-step sequence from commercially available pyrrolidine **3** (Scheme 1). Michael addition of methyl cuprate to the commercially available unsaturated ester **6**, at low temperature resulted in a single *anti* addition product **7**.[14] Osmium tetroxide-mediated dihydroxylation gave *syn* diol **8**. (Sharpless asymmetric dihydroxylation was not chosen because an enantiomeric pure compound was not needed since the *syn* elimination would provide a single dehydration product.) Diol **8** was converted to cyclic sulfate **9** and treated with sodium azide to provide β-hydroxy azide **10**. Hydrogenation of azide **10** to amine **11** and subsequent coupling with acid **5** gave amide **12**, the precursor of the dehydro amino acid moiety.

We screened different EDC(1-ethyl-3-(3-dimethylaminopropyl) carbodiimide)-copper mediated dehydration conditions to introduce the unsaturation and found that copper triflate in THF gave the highest yield and the single desired isomer **13** (Table 1, all the entries gave a single isomer **13**). To our knowledge, this is the first example of preparing a trisubstituted enamide by using this method.

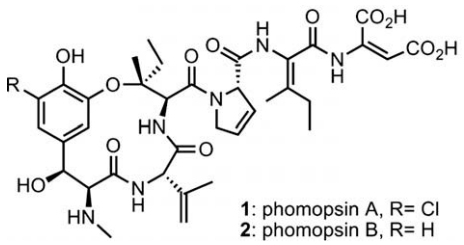

Figure 1. Phomopsins A and B.

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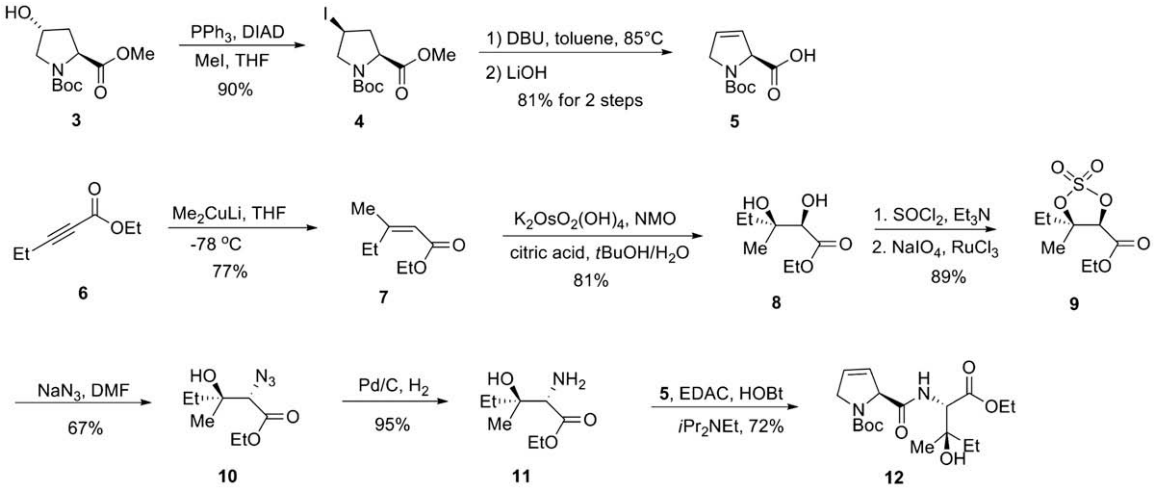
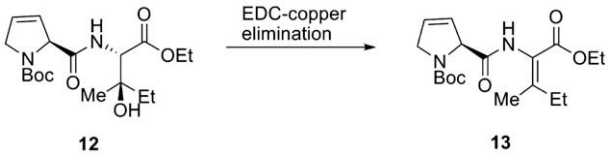


Scheme 1. Preparation of the dehydration precursor.

Table 1
Carbodimide copper dehydration

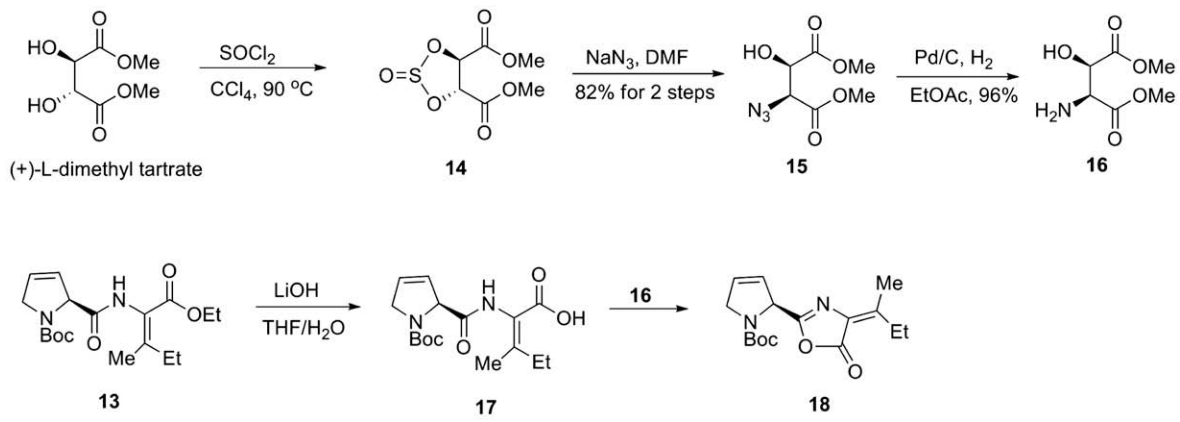


Conditions	Yield (%)
$CuCl_2$, 80 °C, toluene, overnight	11
$CuCl_2$, 100 °C, toluene, 2 h	20
CuI, 100 °C, toluene, 4 h	30
No copper, toluene, 100 °C, overnight	0
$Cu(OTf)_2$, THF, 45 °C, overnight	42
$Cu(OTf)_2$, THF, 60 °C, 1.5 h	73

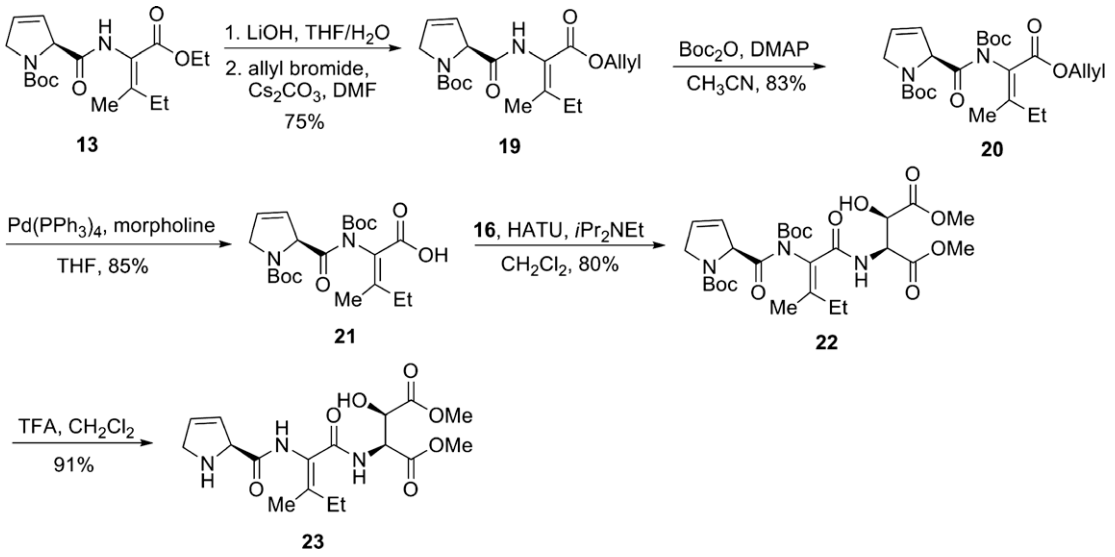
The third amino acid fragment, amine **16**, was prepared by a three-step sequence from commercially available (+)-dimethyl tartrate (Scheme 2).[15] The coupling between acid **17** and amine **16** resulted in the formation of an unreactive azlactone **18**.[7b] To avoid the azlactone formation, the amide nitrogen had to be protected.

Thus, the ethyl ester **13** was converted to allyl ester **19** and the amide nitrogen was protected with Boc to afford compound **20** (Scheme 3). The allyl ester was cleaved under palladium-catalyzed conditions to give acid **21** without reducing the double bond in the dehydroproline moiety.[16] A benzyl ester was also tested but the partial reduction of the double bond occurred under hydrogenolysis conditions. Finally, acid **21** was coupled with amine **16** to give tripeptide **22** and Boc deprotection afforded **23** as the side-chain precursor in the synthesis of phomopsin.[17] As shown by previous workers, the dehydroaspartate unit in the phomopsin side chain isomerizes readily under basic conditions.[18] Compound **23** will be coupled with the macrocycle part of phomopsins A and B directly and the β-hydroxy group will not be eliminated until the final stage of the synthesis.

A highly stereoselective approach to make the (*E*)-dehydroisoleucine moiety of the phomopsin tripeptide side chain was developed to afford the material for the total syntheses of phomopsins A and B. The copper-carbodimide method provides an efficient solution to the stereoselective synthesis of dehydroamino acids. The synthesis and evaluation of the biological activities of phomopsins and their analogues will be reported in due course.



Scheme 2. Preparation of amine **16** and azlactone formation.



Scheme 3. Completion of the side chain precursor.

Acknowledgements

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.072.

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17. *Selected data: compound* **13**: ^{1}H NMR (DMSO-d_6, 70 °C): δ 8.91 (1H, br), 5.97 (1H, m), 5.72 (1H, m), 4.89 (1H, dd, J = 5.1, 2.6 Hz), 4.10 (2H, m), 4.04 (2H, q, J = 7.2 Hz), 2.37 (2H, q, J = 7.5 Hz), 1.39 (9H, s), 1.17 (3H, t, J = 7.2 Hz), 1.02 (3H, t, J =7.5 Hz); ^{13}C NMR (DMSO-d_6, 70 °C): δ 167.8, 163.8, 152.7, 144.6, 127.4, 125.7, 121.9, 78.5, 66.9, 59.2, 53.1, 27.6, 26.0, 18.0, 13.4, 12.1; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_5$ (M+H$^+$): 353.2076, found (M+H$^+$): 353.2091; IR (cm^{-1}): 3273 (w), 2977(m), 1709 (s), 1520 (w), 1401 (s), 1207 (w), 1105(w); $[\alpha]_D^{25}$ −160 (*c* 1.96, $CHCl_3$). Compound **23**: ^{1}H NMR ($CDCl_3$): δ 9.22 (1H, br), 6.84 (1H, d, J = 7.8 Hz), 5.92 (2H, m), 5.19 (1H, dd, J = 7.9, 2.7 Hz), 4.80 (1H, d, J = 2.8 Hz), 4.69 (1H, m), 4.02 (1H, m), 3.87 (1H, m), 3.81 (1H, s), 3.74 (1H, s), 2.38 (2H, q, J = 7.6 Hz), 1.74 (3H, s), 1.10 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$): δ 172.0, 171.7, 170.0, 165.6, 129.2, 127.8, 124.0, 123.6, 71.1, 68.9, 56.2, 54.4, 52.7, 52.5, 26.9, 17.3, 12.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{26}N_3O_7Na$ (M+H$^+$): 384.1701, found (M+Na$^+$): 384.1765; IR (cm^{-1}): 3288 (w, br), 2958 (w), 1748 (s), 1661 (s), 1514 (s), 1439(w), 1223 (m), 1125 (m), 1029 (w); $[\alpha]_D^{19}$ −76 (*c* 0.21, $CHCl_3$).
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