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Synthetic Studies Towards Keramamide F

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Abstract: This communication describes the synthesis of three fragments of the cytotoxic natural product keramamide F.

Keramamide F (KF)[1] is a cytotoxic natural product found in small quantities in *Theonella* sponge.[2] This cyclic peptide contains a remarkable array of unusual amino acids including a didehydrotryptophan, an *O*-methylserylthiazole derivative, an isoserine residue, and an α-ketoamide function as part of the amino acid 3-amino-4-methyl-2-oxo-hexanoic acid. These structural features, and an interest in obtaining KF for biophysical and biochemical studies, stimulated us to embark upon a total synthesis of this compound. We envision a synthesis of KF from the three fragments shown in Figure **1**. These fragments are anticipated to provide access to the final product *via* a convergent route that avoids the possible complication of C-terminal epimerization upon ring closure. This communication describes the synthesis of fragments **1**, **2** and **3**.

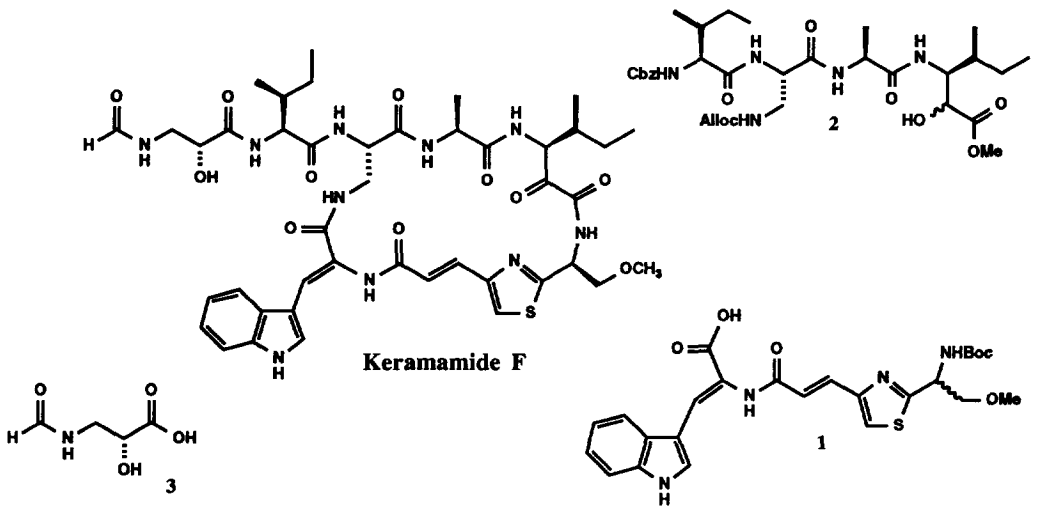
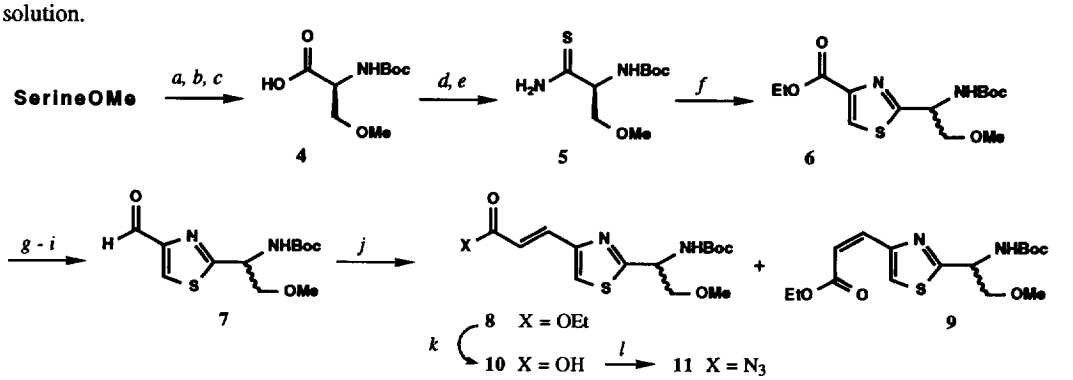


Figure **1**. The natural product, keramamide F, will be assembled from three fragments **1**, **2**, and **3**.

In considering approaches to fragment **1** we chose to take advantage of the well-studied Hantzsch reaction[3] for construction of the thiazole. The thiazole precursor, **5**, was prepared in five steps from serine

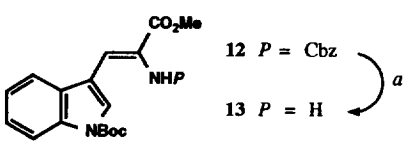
methyl ester as shown in Scheme **1**, and condensed with α-bromopyruvate in ethanol to obtain the thiazole ester **6** as a racemic mixture. Optically active (*O*-methylseryl)thiazole **6** can be obtained using the modified conditions described by Holzapfel.[4] However, removal of the Boc protecting group using TFA and formation of the MTPA amides indicates that compound **6** is still a 4:1 mixture of enantiomers. No further improvement upon this ratio has been achieved under any conditions, including the those recently reported by Meyers and coworkers.[5] Methods for separating the enantiomers and for determining the absolute stereochemistry of the major isomer are under investigation.

Ester **6** was converted in three steps to aldehyde **7** which was immediately reacted with carboethoxymethylenetriphenylphosphorane in the presence of 1.1 equivalents of LiCl to produce the readily separable *E*- and *Z*- enoates **8** and **9** in a 20:1 ratio. The double bond geometry for each enoate was assigned based on NMR coupling constants of 15.4 Hz and 10.5 Hz for the vinylic protons in compounds **8** and **9** respectively. Enoic acid **10** was obtained from enoate **8** by saponification in methanolic sodium hydroxide solution.



Scheme **1**. *a*. $(Boc)_2O$, Et_3N, 97%. *b*. Me_3OBF_4, proton sponge. c. NaOH, MeOH. *d*. i. *iso*-Butylchloroformate, NMM, ii. $NH_3(g)$, DME, 56% over 3 steps. *e*. Lawesson's reagent, DME, 84%. *f*. ethyl bromopyruvate, K_2CO_3, TFAA, pyridine, 70%. g. NaOH, MeOH, 92%. *h*. HN(OMe)Me, BOP, Et_3N, CH_2Cl_2, 85%.[6] *i* . $LiAlH_4$, THF-Et_2O, 60%. *j*. $(Ph)_3P{=}CHCO_2Et$, LiCl, 90%. *k*. NaOH(aq), MeOH. *l*. DPPA, Et_3N, CH_2Cl_2, 81%.

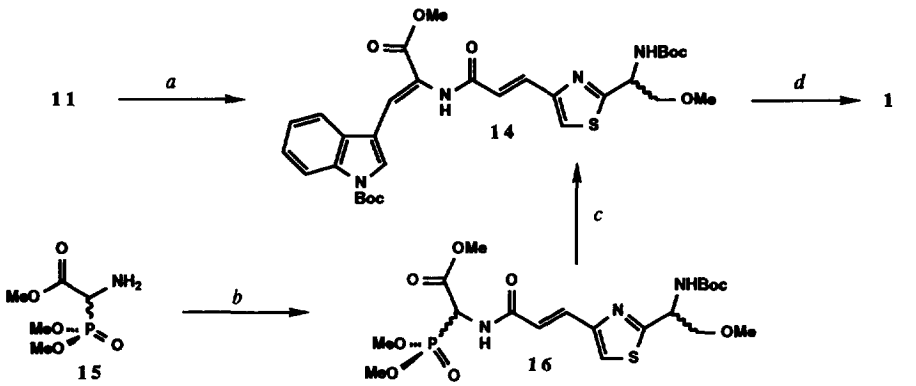
Incorporation of the didehydrotryptophan has been achieved in two ways. *N*-Cbz-*N'*-Boc-*Z*-α,β-didehydrotryptophan was prepared as described by Schmidt and coworkers[7] and hydrogenolyzed using ammonium formate and palladium on carbon in aqueous dimethylformamide to remove the benzyloxycarbonyl protecting group, providing enamine **13** (Scheme **2**). This enamine could be readily acylated with simple electrophiles such as benzyloxycarbonyl chloride, but resisted formation of an amide bond with enoic acid **10** under a variety of conditions and reagents.[8]



Scheme **2**. *a*. Pd/C, NH_4HCO_2, 70%.

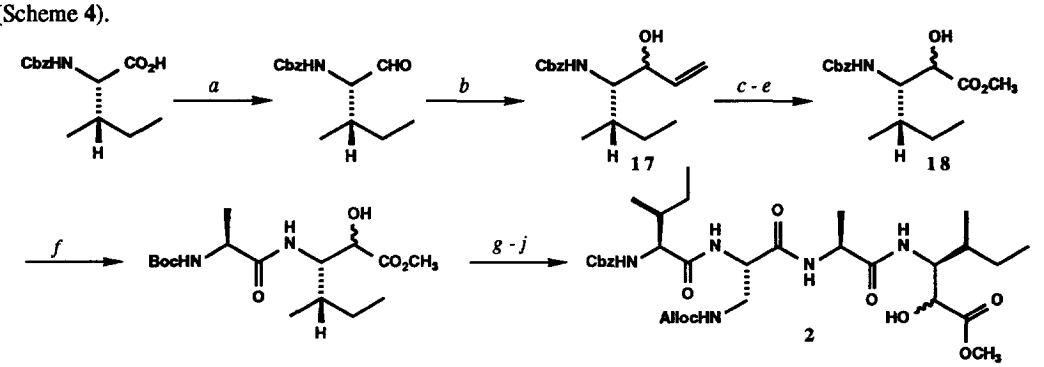
Eventually, it was found that the enamine anion, formed from **13** using LHMDS, could be acylated with the acylazide **11** (Scheme **1**) to give the product amide **14** in approximately 30% yield (Scheme **3**). Alternatively, trimethylphosphonoglycine (**15**)[9] can be condensed with enoic acid **10** using BOP, and the resulting phosphonate **16** undergoes a Horner-Wadsworth-

Emmons reaction with *N*-Boc-indole 3-carboxaldehyde to give **14** as a separable mixture of *E* and *Z* isomers (4:1, 33%; Scheme **3**). Fragment **1** is obtained from the ester **14** by saponification using methanolic NaOH solution with concomitant loss of the indole Boc group.



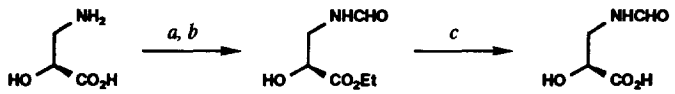
Scheme **3**. *a*. **13**, LHMDS, THF, 35%. *b*. **10**, BOP, Et_3N, CH_2Cl_2, 56%. *c*. i. KDA, THF, ii. *N*-Boc-indole 3-carboxaldehyde, 26%. *d*. NaOH, MeOH, 92%.

Synthesis of the second fragment required for KF proceeded in a straightforward manner as shown in Scheme **4**. Reduction of *N*-Cbz-L-isoleucine to the corresponding aldehyde, followed by the addition of vinylmagnesium bromide provided allylic alcohol **17** as a 4:1 mixture of diastereomers which were not separated. Ozonolysis of **17** followed by oxidation to the acid and esterification provided hydroxy ester **18**. This residue was extended using standard peptide coupling reactions to produce the desired fragment, **2** (Scheme **4**).



Scheme **4**. *a*. i. HN(OMe)Me, BOP, Et_3N, CH_2Cl_2, 87%, ii. $LiAlH_4$, THF-Et_2O, 86%. *b*. $CH_2CHMgBr$, THF, *c*. O_3, MeOH, ii. Me_2S, MeOH. *d*. $NaClO_2$, NaH_2PO_4, $H_2C{=}C(CH_3)_2$, H_2O. *e*. CH_2N_2, Et_2O, 35% over 4 steps. *f*. i. H_2, Pd/C, ii. Boc-Ala, BOP, Et_3N, CH_2Cl_2, 95%. *g*. TFA-CH_2Cl_2. *h*. *N*-Boc-*N'*-alloc-β-amino-L-alanine, BOP, Et_3N, CH_2Cl_2. *i*. TFA-CH_2Cl_2. *j*. Cbz-L-isoleucine, BOP, Et_3N, CH_2Cl_2, 46% over 4 steps.

For the remaining fragment, isoserine was prepared from L-malic acid as described by Maeda and coworkers[10] and esterified in ethanolic HCl. The ethyl ester was formylated with formic acid and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDCI). Saponification of this compound gives fragment **3**.



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Scheme **5**. *a*. HCl(g), EtOH. *b*. HCO_2H, EDCI, NMM, CH_2Cl_2, 16% over 2 steps. *c*. LiOH, dioxane, 100%.

In conclusion, synthetic routes to fragments **1**, **2**, and **3**, required for a total synthesis of KF, are now established. Coupling of these fragments, and characterization of the final product will be reported shortly.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. Abbreviations used in this manuscript: Alloc, allyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; BOP, benzotriazolyl-yloxy-tris(dimethylamino-phosphonium) hexafluorophosphate; Cbz, benzyloxycarbonyl; DME, dimethoxyethane; DPPA, diphenylphosphoryl azide; EDCI, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide; KDA, potassium diisopropylamide; KF, keramamide F; LHMDS, lithium hexamethyldisilazide; NMM, 4-methylmorpholine; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran.
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