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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 reaction³ 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, Et₃N, 97%. b. Me₃OBF₄, proton sponge. c. NaOH, MeOH. d. i. iso-Butylchloroformate, NMM, ii. NH₃(g), DME, 56% over 3 steps. e. Lawesson's reagent, DME, 84%. f. ethyl bromopyruvate, K₂CO₃, TFAA, pyridine, 70%. g. NaOH, MeOH, 92%. h. HN(OMe)Me, BOP, Et₃N, CH₂Cl₂, 85%.⁶ i. LiAlH₄, THF-Et₂O, 60%. j. (Ph)₃P=CHCO₂Et, LiCl, 90%. k. NaOH(aq), MeOH. l. DPPA, Et₃N, CH₂Cl₂, 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 coworkers⁷ 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



Scheme 2. a. Pd/C, NH₄HCO₂, 70%.

bond with enoic acid 10 under a variety of conditions and reagents.⁸

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-WadsworthEmmons 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, Et₃N, CH₂Cl₂, 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, Et₃N, CH₂Cl₂, 87%, ii. LiAlH₄, THF-Et₂O, 86%. b. CH₂CHMgBr, THF, c. O₃, MeOH, ii. Me₂S, MeOH. d. NaClO₂, NaH₂PO₄, H₂C=C(CH₃)₂, H₂O. e. CH₂N₂, Et₂O, 35% over 4 steps. f. i. H₂, Pd/C, ii. Boc-Ala, BOP, Et₃N, CH₂Cl₂, 95%. g. TFA-CH₂Cl₂. h. N-Boc-N-alloc- β -amino-L-alanine, BOP, Et₃N, CH₂Cl₂. i. TFA-CH₂Cl₂. j. Cbz-L-isoleucine, BOP, Et₃N, CH₂Cl₂, 46% over 4 steps.

For the remaining fragment, isoserine was prepared from L-malic acid as described by Maeda and coworkers¹⁰ 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.



Scheme 5. a. HCl(g), EtOH. b. HCO₂H, EDCI, NMM, CH₂Cl₂, 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.

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REFERENCES AND NOTES

- 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-ethylcarbodiimide; KDA, potassium diisopropylamide; KF, keramamide F; LHMDS, lithium hexamethyldisilazide; NMM, 4-methylmorpholine; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran.
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