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# Total Synthesis of Kapakahine E and F

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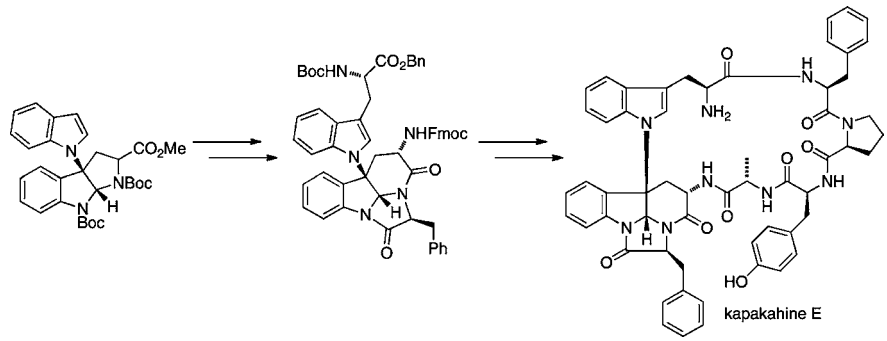
## ABSTRACT




**The total synthesis of the cyclic peptides kapakahine E and F using bromopyrroloindoline heterodimerization reactions, indoline to α-carboline rearrangements, and Negishi coupling reactions is described.**

The kapakahine family of cyclic peptides was isolated from the marine sponge *Cribrochalina olemda* by Nakao, Scheuer, and co-workers.[1−3] The members of this family have in common a C(3)−N(1′) dimeric tryptophan linkage where one of the residues has rearranged to an α-carboline and differ from one another in the remaining amino acid residues or, in the cases of kapakahines A, C, and D, in whether the indole of the non-α-carboline tryptophan residue has undergone an oxidative cyclization (Figure 1). Whereas extensive NMR experiments and degradation studies were used to assign the structures of kapakahines A−D and F, because of their limited supply the structures of kapakahines E and G were assigned on the basis of the similarities of their NMR spectra to kapakahines A and B and on MS experiments (FABMS and FAB MS/MS).

Although a thorough evaluation of the properties of this family has not been carried out, preliminary cytotoxicity data showed that kapakahines A, B, C, and E were the most active against P388 murine leukemia cells with in vitro $IC_{50}$ values of ca. 5.0 $\mu$g/mL. On the basis of their unique structures, unknown biological activity, and limited supply it is not surprising that the kapakahine family has received attention from the synthetic community. Along these lines, Baran and co-workers recently reported an elegant total synthesis of kapakahines B and F where they employed their oxidative coupling chemistry in a key step.[4]

We also became interested in the synthesis of members of this family. The focal point of our approach was the generation of a tryptophan C(3)−N(1′) heterodimer **2** that would come from the coupling of bromoindoline **3** and the appropriate tryptophan derivative. From **2**, rearrangement of the indoline to the corresponding α-carboline and imidazolone formation would give C(3)−N(1′) heterodimer **1**. Upon its formation we anticipated that **1** would serve as a general precursor to all of the known kapakahine natural products. From Baran's analysis of the generation of the α-carboline, a potential problem with this idea was the presumed instability of **1**.[4,5] We hoped that the judicious choice of amine protecting groups would enable us to overcome this problem if and when it arose.

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(3) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *Org. Lett.* **2003**, *5*, 1387–1390.
(4) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360–6361.
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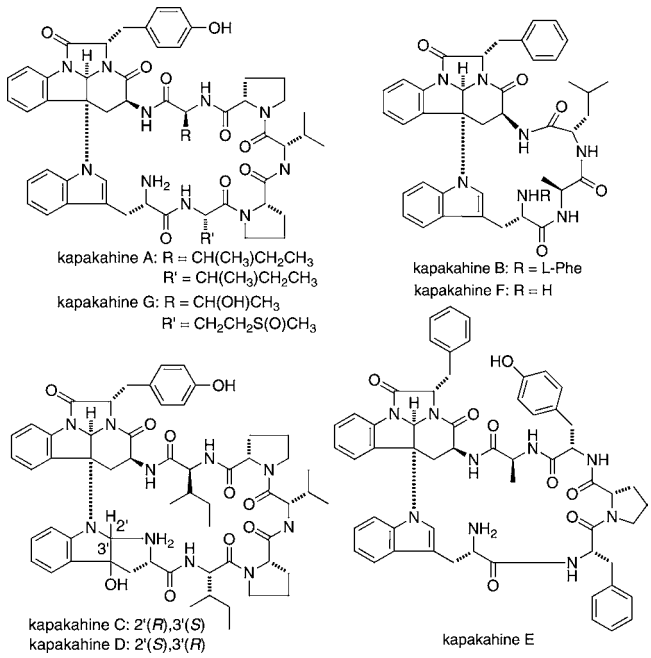
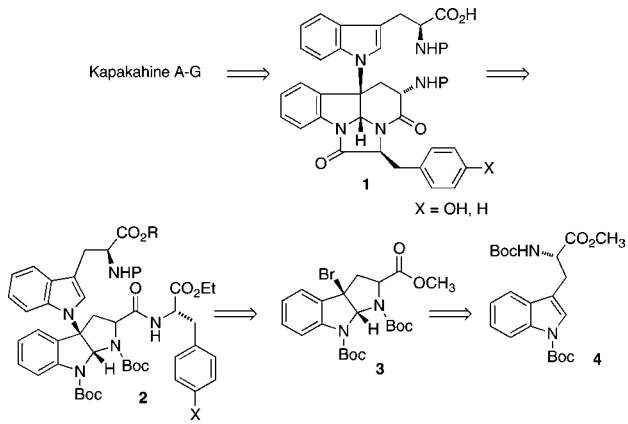


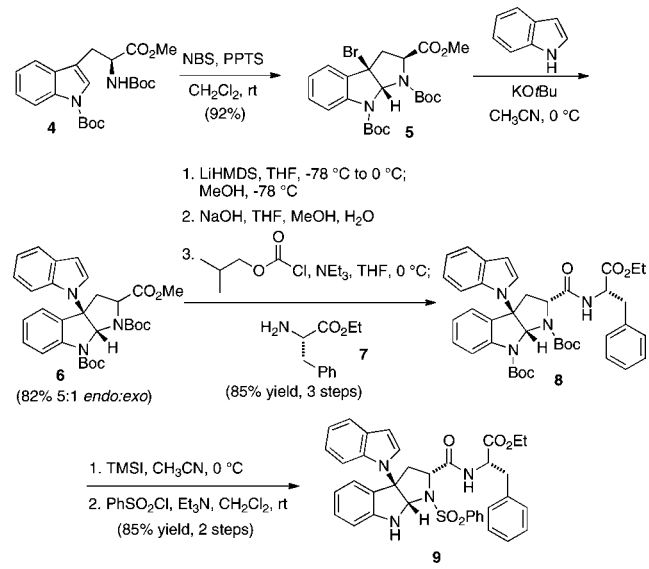

**Figure 1.** Kapakahine natural products.

As outlined in Scheme 2 for the generation of **6** from the coupling of bromopyrroloindoline **5** with indole under basic conditions, we have previously developed an efficient and direct approach to pyrroloindoline dimers.[6] Thus, our initial focus with respect to the synthesis of the kapakahine family was on the pyrroloindoline to α-carboline transformation. To this goal we decided to test whether the conditions used by Sunazuka, Õmura, and co-workers that involved the use of $Me_3Al$ to effect the conversion of an *N*,*O*-aminal into an α-carboline could be used to solve the related pyrroloindoline to α-carboline transformation.[7] We found it best to work with a single pyrroloindoline dimer and converted *exo*-**6** into *endo*-**6** through the kinetic protonation protocol illustrated.[8] Subsequently, hydrolysis of the ester and dipeptide formation gave **8** in 85% yield. Removal of both Boc groups with TMSI and selective sulfonamide formation provided model rearrangement precursor **9** in high yield.

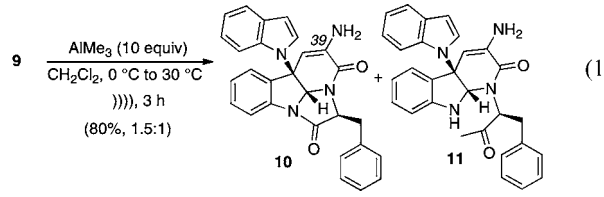
**Scheme 1.** Retrosynthetic Analysis of Kapakahines




**Scheme 2.** Synthesis of Pyrroloindoline **9**



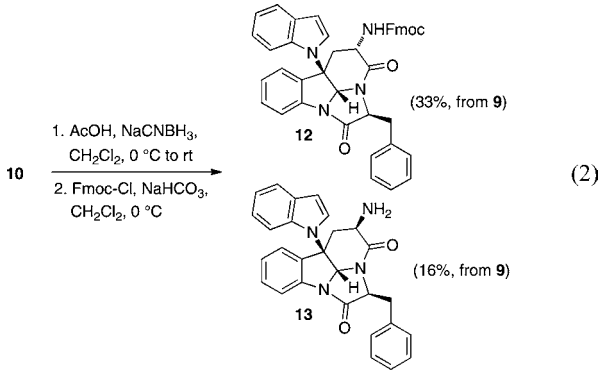

With **9** in hand, we examined α-carboline formation and were delighted to isolate model **10** from a mixture of products when **9** was exposed to Sunazuka and Õmura's conditions and $AlMe_3$ (eq 1). Interestingly, not only had **10** undergone the desired α-carboline and imidazolone forming reactions, elimination of phenylsulfinic acid had occurred to give the corresponding enamine. Our interest in this latter development was a consequence of the fact that in the absence of the phenylsulfinic acid elimination, the rearrangement of **9** would have delivered the undesired stereochemistry at C(39) (kapakahine E numbering system). A stereoselective reduction of **10** from the *exo*-face would deliver the desired kapakahine stereochemistry. After optimization it was found that a combination of sonication and slightly elevated temperature gave **10** as the major product of a mixture consisting of **10** and methyl ketone **11**, presumably a result of the reaction of the imidazolone ring in **10** with $AlMe_3$. In contrast to Baran's kapakahine work, we did not isolate any pyrroloindoline from the reaction of **9** with $AlMe_3$.




(1)

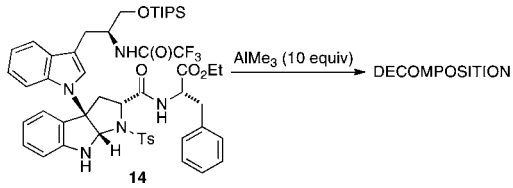
As planned, we were able to establish the desired C(39) stereochemistry by subjecting **10** to reductive conditions in the presence of AcOH to give **12** after Fmoc protection (eq 2).[9] To our dismay, accompanying α-carboline **12** was a considerable amount of diastereomeric α-carboline **13**.

Despite this, that **12** was generated in only 3 steps from indoline heterodimer **9** in a synthetically useful 33% overall yield has enabled us to proceed in our kapakahine E and F studies.



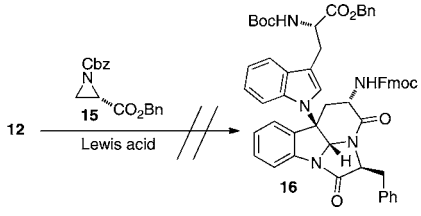
(2)

With a method to the desired α-carboline and imidazolone rings in hand with model substrate **12**, we next explored the $AlMe_3$ reaction on bis-tryptophan heterodimers (eq 3). Representative of the substrates examined in these studies was heterodimer **14** where only uncharacterizable mixtures of products were observed when **14** was subjected to the conditions that had been successful for **9**.



(3)

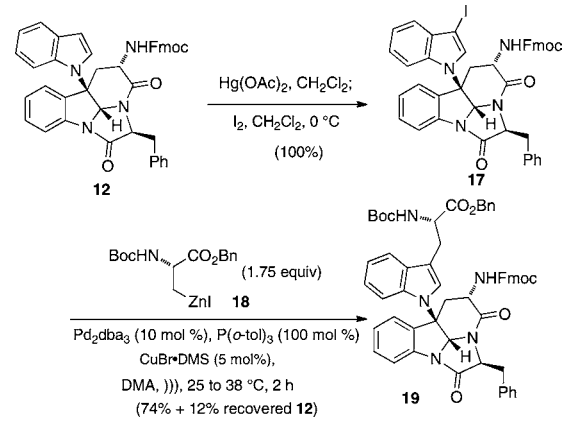
Our lack of success in the rearrangement of **14** forced us to revise our approach and to consider the introduction of the tryptophan side chain subsequent to α-carboline formation. Methods of carrying out such a conversion include aziridine ring openings,[10] conjugate additions,[11] and Heck coupling reactions.[12] Because it would enable us to incorporate the side chain directly, our initial focus was on the use of the aziridine ring-opening reaction to convert **12** into **16** (eq 4). Unfortunately, all attempts at this reaction were unsuccessful, resulting in either the recovery of **12** or its decomposition into unidentifiable mixtures of products.



(4)

With the failure of the aziridine chemistry and our perception that the conjugate addition and Heck approaches would lead to indirect solutions to the problem, we turned our attention to the development of a new method of introducing the side chain and settled upon the use of a Negishi coupling reaction between known Zn alanine derivative **18** and iodoindole **17** (Scheme 3). Although **18** had been widely employed in coupling reactions with aromatic and vinylic halides and triflates,[13] to the best of our knowledge it had not been used in the synthesis of tryptophan derivatives.[14] To examine tryptophan formation, we synthesized iodoindole **17** from **12** and then exposed **17** to **18** and the conditions illustrated. Pleasingly, **17** underwent the desired coupling reaction to give desired tryptophan heterodimer **19** in 74% yield, effectively completing our synthesis of the kapakahine dimeric tryptophan core.

**Scheme 3.** Completion of the Synthesis of the Kapakahine Bis-Trp Core




With **19** in hand we were positioned to examine our hypothesis that it would serve as a general precursor to the kapakahine natural products. To kapakahine E, the coupling of **19** with the requisite L-Phe-L-Pro-L-Tyr-L-Ala tetrapeptide **20** involved first subjecting **19** to hydrogenolysis conditions at low temperature to selectively remove the benzyl ester in the presence of the Fmoc group (Scheme 4). EDCI, HOBt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(13) For leading references, see: (a) Ross, A. J.; Lang, H. L.; Jackson, R. F. W. *J. Org. Chem.* **2010**, *75*, 245–248. (b) Dexter, C. S.; Jackson, R. F. W.; Elliott, J. *J. Org. Chem.* **1999**, *64*, 7579–7585. (c) Jackson, R. F. W.; Moore, R. J.; Dexter, C. S.; Elliott, J.; Mowbray, C. E. *J. Org. Chem.* **1998**, *63*, 7875–7884. (d) Sakai, R.; Koike, T.; Sasaki, M.; Shimamoto, K.; Oiwa, C.; Yano, A.; Suzuki, K.; Tachibana, K.; Kamiya, H. *Org. Lett.* **2001**, *3*, 1479–1482.

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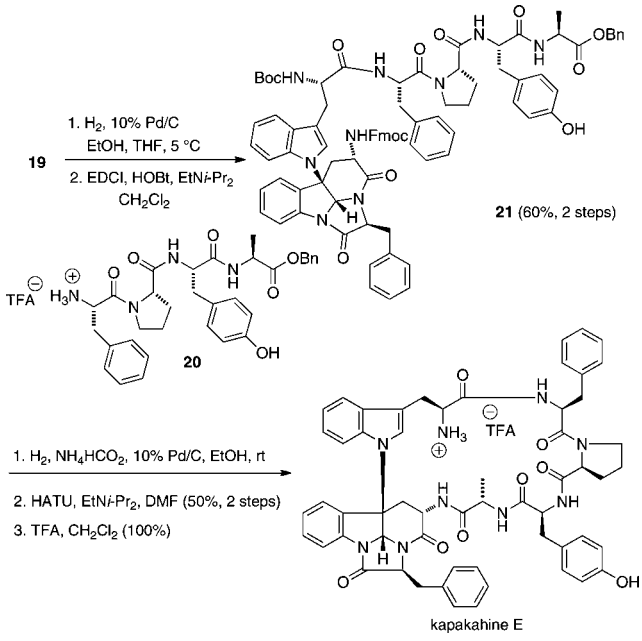
coupling with **20** gave amino ester **21**. Hydrogenolysis of the Fmoc and benzyl groups and cyclization gave Boc-protected kapakahine E. Deprotection provided the TFA salt of kapakahine E.

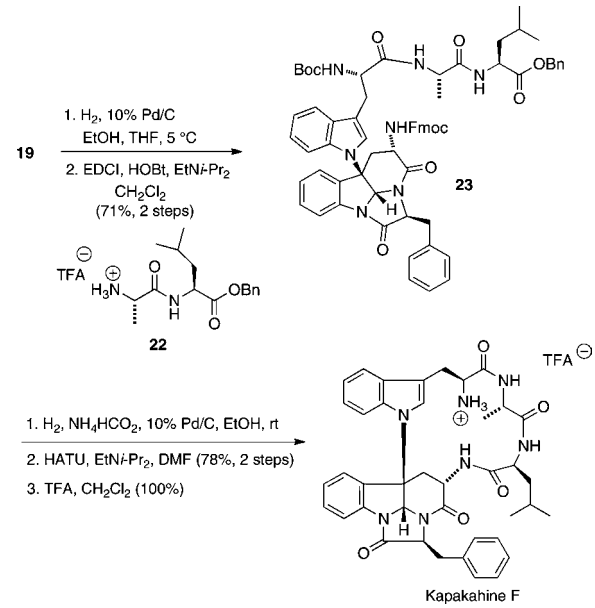
Professor Yoichi Nakao (Waseda University) graciously provided us with a 0.1 mg sample of kapakahine E that was used in a series of comparative LC−MS/MS experiments with our synthetic material. These studies showed that the natural and synthetic kapakahine E had identical LC retention times and MS/MS fragmentation spectra. On the basis of this, our NMR data ($^1$H, $^{13}$C, COSY, HMQC, NOE), and our synthesis of kapakahine F, vide infra, we are confident that we have synthesized kapakahine E, thus confirming its original structure as proposed by Nakao, Scheuer and co-workers.[3]

**Scheme 4.** Completion of the Synthesis of Kapakahine E




We employed a nearly identical sequence to that used for the synthesis of kapakahine E to synthesize kapakahine F (Scheme 5). Coupling of **19** with L-Ala-L-Leu-OBn dipeptide **22** gave **23**. Deprotection of the Fmoc and benzyl groups, cyclization, and deprotection gave kapakahine F in five steps from **19**. Our kapakahine F spectral data ($^1$H NMR, $^{13}$C NMR, MS) matched that reported by Baran and co-workers in their studies.[4]

**Scheme 5.** Completion of the Synthesis of Kapakahine F




In conclusion, the combination of bromoindoline heterodimerization reactions, pyrroloindoline to α-carboline rearrangements, and Negishi coupling reactions has resulted in what we believe is a general approach to the kapakahine family of natural products. This manuscript has described the use of this sequence for the synthesis of kapakahines E and F. Current work in our laboratory is focused on both the synthesis of the other members of the family and related analogs.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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