# Total Synthesis and Complete Structural Assignment of Yaku'amide A

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## 1. Introduction

### 1-1 Background

- Marine sponges are rich sources of structually unusual and biologically active peptides.

→ Yaku'amide A was isolated from the deep-sea sponge *Ceratopsion* sp. by Matsunaga et al.[1]

- Author's motivation: its unique highly unsaturated structure and its cytotoxicity profile.

→ This tridecapeptide consists of 2 proteinogenic* and 11 nonproteinogenic amino acid residues and is capped with a *N*-terminal acyl group (NTA) and a C-terminal amine (CTA).

* Proteinogenic amino acids are precursors to proteins.

→ It exhibited extremely potent cytotoxicity and growth inhibitory profile against a panel of 39 human cancer cell lines (JFCR39) that include various human cancers.

### 1-2 Challenges

- Challenge: The stereoselective synthesis of *E*- and *Z*-$\alpha, \beta$– dehydroisoleucine moieties

  …$\alpha, \beta$– unsaturated amino acids (❶, ❷, ❸, and ❹)

  Previous reports: × a mixture of *E*- and *Z*-isomers (Shin et al)[2]

  × harsh conditions, highly toxic reagents (Wandless et al, Joullie et al)[2]

- The absolute configuration at C4 of the *N*-terminal acyl group (NTA) was not elucidated.

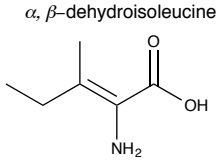
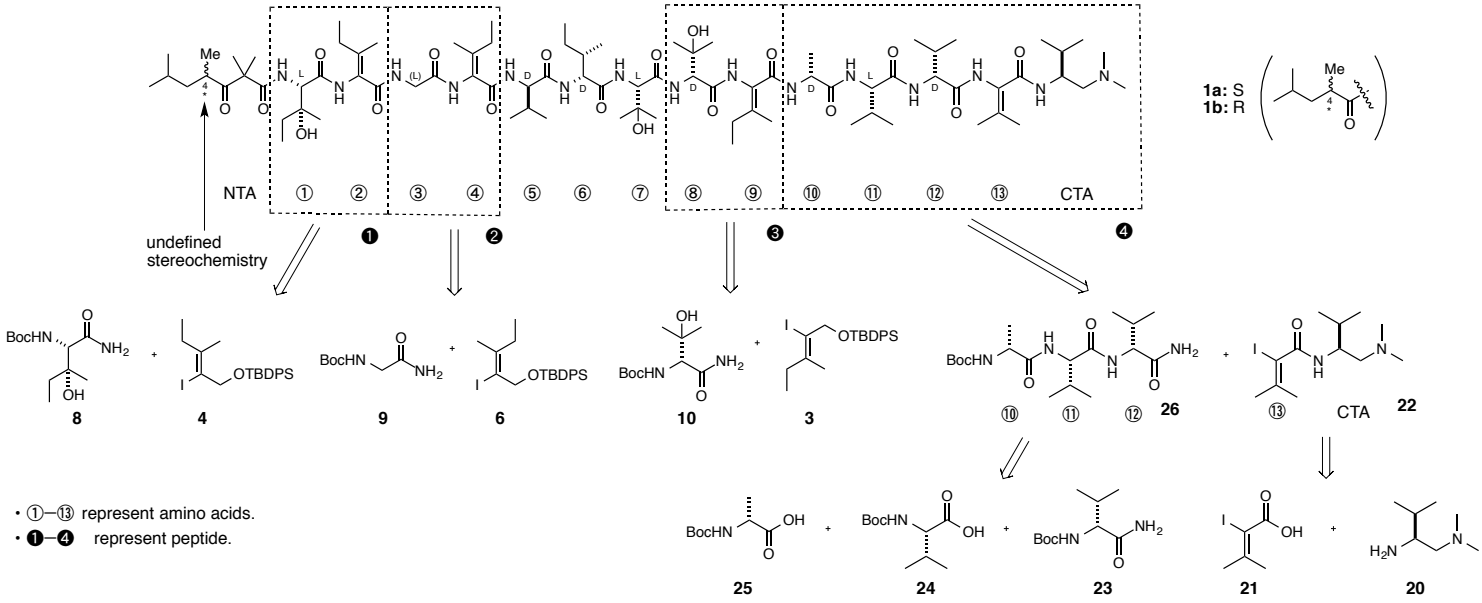



***Figure 1.***

### 1-3 Ideas of This Work

- Enabler: Cu-catalyzed cross coupling reactions for *E/Z* selective synthesis

***Scheme 1. Structure of Yaku'amide A (1a and 1b) and synthetic strategies***




- To determine the absolute C4-stereochemistry, they planned to construct two possible C4 isomers and then compare them with the natural **1**.

## 2. Results and Discussion

### 2-1 Synthesis of ❶, ❷, and ❸

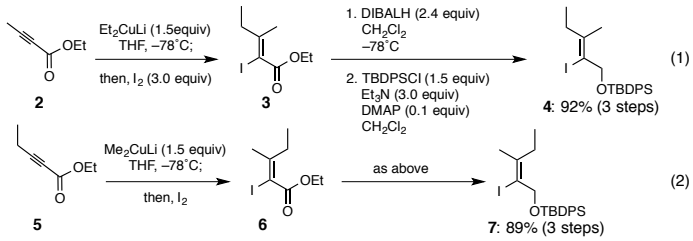
#### 2-1-1 Stereoselective synthesis of *E*- and *Z*-alkenyl iodide monomers (Scheme2)

*Scheme 2.*

→ A conjugate addition of lithium dialkylcuprate and in situ trapping with iodine delivered *E*/*Z*-olefin.

→ Reduction with DIBALH and protection with TBDPS group furnished *E*/*Z*-alkenyl iodide.

*The geometries of the double bonds of products were confirmed by nuclear Overhauser effect (NOE).

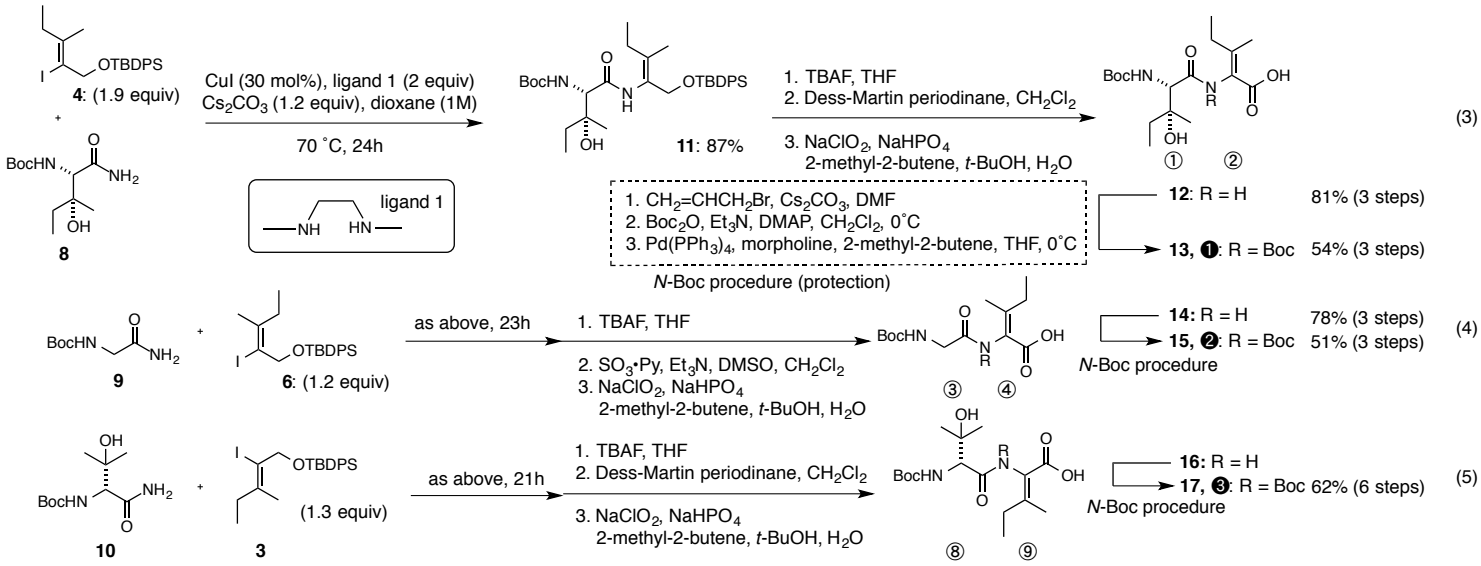



#### 2-1-2 Mild Cu-catalyzed cross-coupling methods for synthesis of ❶, ❷, and ❸

- Enabler: Buchwald reagent system [CuI, *N, N'*-dimethylethylenediamine, $Cs_2CO_3$][3]

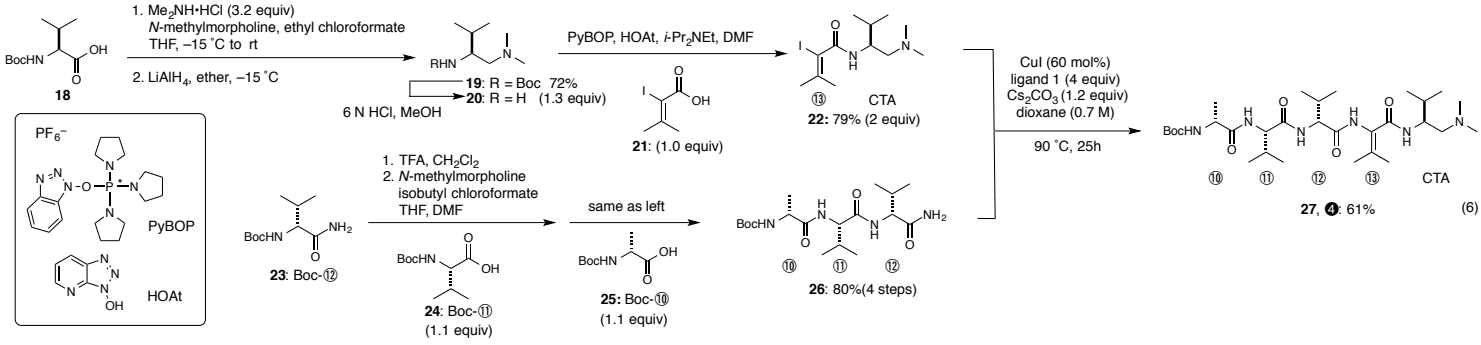
→ Cu catalyst and $Cs_2CO_3$ promoted stereoselective substitution of iodine of Z-alkenyl iodide, producing the corresponding *Z*-enamides.

***Scheme 3. Stereoselective synthesis of E- and Z-dehydroisoleucine moieties***




### 2-2 Synthesis of ❹

***Scheme 4. Synthesis of C-terminal tetrapeptide***

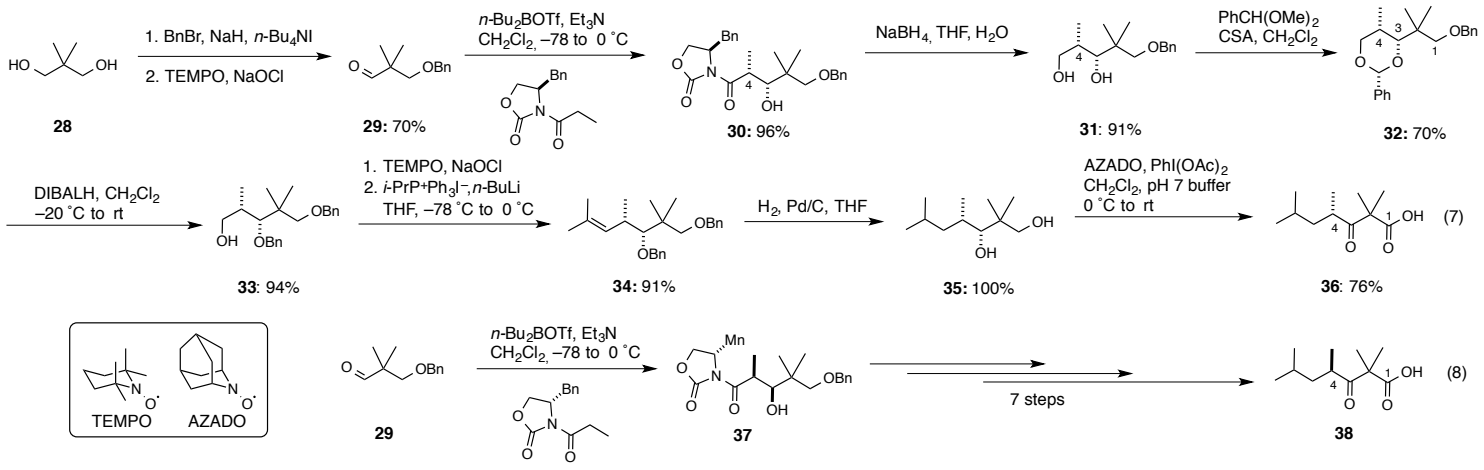


## 2-3 Synthesis of NTA (N-terminal acyl group)

- The C4-stereochemistries of S/R-isomers were installed using the Evans asymmetric aldol reaction.

→ Mild conditions eliminated the risk of C4-epimerization and C1-decarboxylation

***Scheme 5. Synthesis of two enantiomeric NTAs***

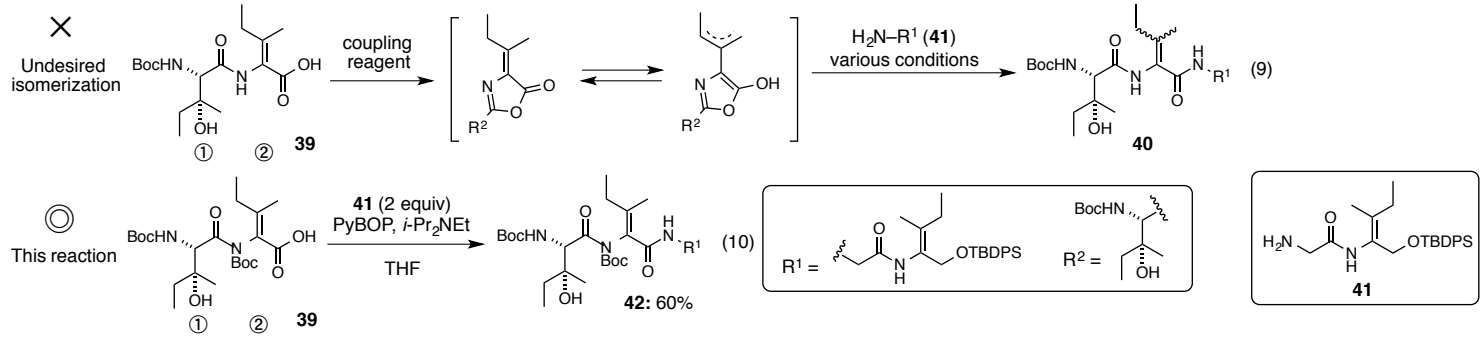



## 2-4 Total synthesis of Yaku'amide A

- Challenge: isomerization of *Z*-dehydroisoleucine acid during amidation.

→ They prevented the isomerization by protecting the secondary amide with a Boc group (Scheme 6).

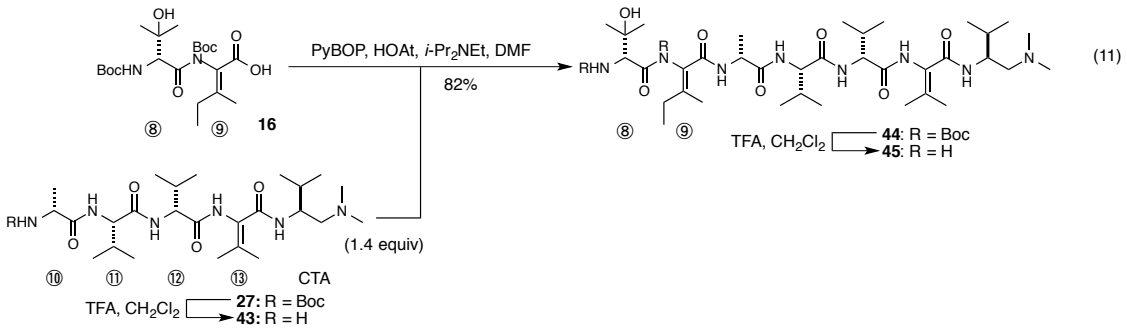
***Scheme 6. Model study for isomerization-free amidation of α, β–dehydroisoleucine***




- Finally, multiple amide bond formations completed the total synthesis (Scheme 7).

→ They synthesized the target molecule, Yaku'amide A, through repeating the seven Boc-removal/condensation procedures from ❹ (Scheme 7).

***Scheme 7. Total synthesis of two possible isomers of yaku'amide A***

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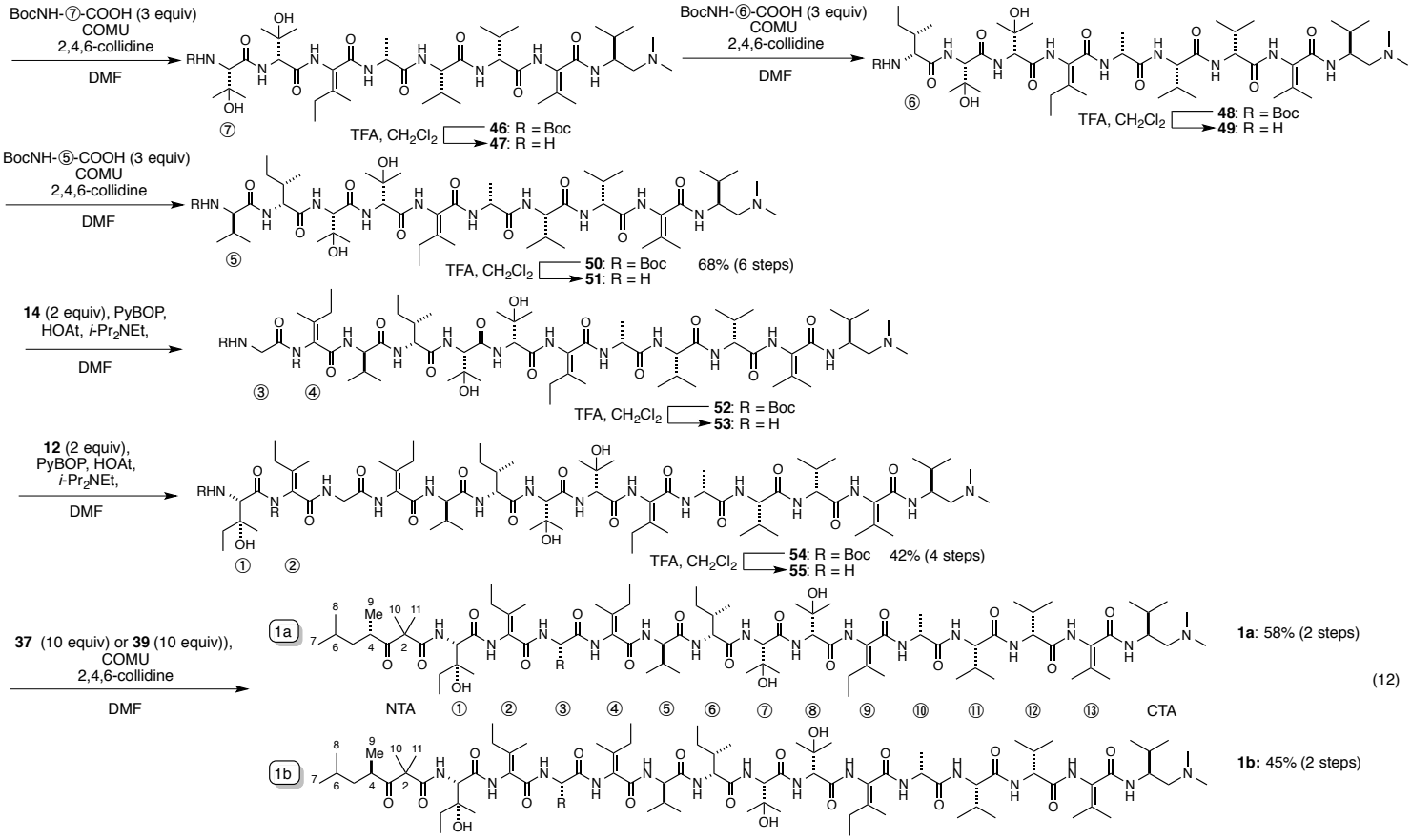


3. **Stereochemistry and Biotoxicity**

- The complete structure of Yaku'amide A was confirmed as **1a** by NMR analysis.

→ Possessed the C4-S-stereochemistry of **1a**

- Preliminary toxicity study using mouse leukemia P388 cells

→ Both **1a** and **1b** displayed similar $IC_{50}$ values.
(cf) $IC_{50}$ value of 1a: 24 nM, 1b: 83 nM, natural product: 46 nM

→ The effect of the C4-stereocenters on the potent toxicity of **1** was small.

## 4. Conclusion

- First total synthesis of Yaku'amide A was accomplished.
- Determination of the complete stereochemical structure of yaku'amide A to be **1a** with the C4 S-stereochemistry.
- Discover the relationship between stereochemistry of C4 and cytotoxicity.

## 5. References

(1) Ueoka, R.; Ise, Y.; Ohtsuka, S.; Okada, S.; Yamori, T.; Matsunaga, S. *J. Am. Chem. Soc.* **2010**, *132*, 17692-17694.

(2) (a) Nakamura, Y.; Ito, A.; Shin, C. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2151, (b) Stohlmeyer, M. M.; Tanaka, H.; Wandless, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 6100, (c) Shangguan, N.; Joullie, M. *Tetrahedron Lett.* **2009**, *50,* 6748.

(3) (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421, (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5,* 3667.