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Convergent Total Synthesis of Yaku'amide A

Yu Cai, Zhiwei Ma, Jintao Jiang, Concordia C. L. Lo, Shi Luo, Ankur Jalan, Joseph M. Cardon, Alexander Ramos, Diego A. Moyá, Daniel Joaquin, and Steven L. Castle*

Abstract: Total synthesis of the anticancer peptide natural product yaku'amide A is reported. Its β-*tert* hydroxy amino acids were prepared via regioselective aminohydroxylation involving a chiral mesyloxycarbamate reagent. Stereospecific construction of the *E*- and *Z*-ΔIle residues was accomplished via a one-pot reaction featuring *anti* dehydration, azide reduction, and O→N acyl transfer. Alkene isomerization was negligible during this process. These methods enabled a highly convergent and efficient synthetic route to the natural product.

Yaku'amides A and B (**1** and **2**, Figure 1) are linear peptides that were isolated in minute quantities by Matsunaga and co-workers from *Ceratopsion sp.*, a deep-sea sponge found in the East China Sea.[1] They are comprised of thirteen amino acids including four dehydroamino acids (ΔAAs) and three β-hydroxy amino acids (β-OHAAs), an *N*-terminal acyl group (NTA), and a *C*-terminal amine (CTA). The NTA stereochemistry was undefined at the time of isolation. The presence of both *E*- and *Z*-ΔIle is noteworthy; whereas the former is found in a select group of natural products,[2] **1** and **2** are the first known metabolites to contain the latter. Screening of **1** against the JFCR39 cancer cell line panel[3] revealed a unique pattern of activity, which is suggestive of a novel mode of action.

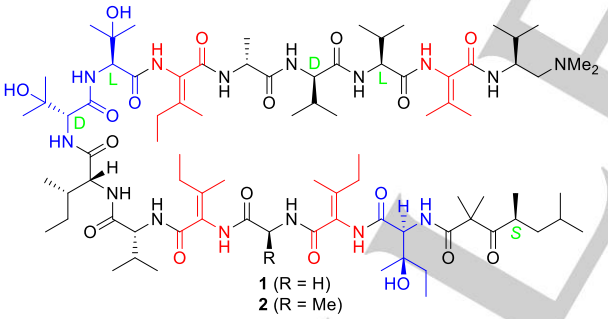

Figure 1. Yaku'amides A (**1**) and B (**2**). ΔAAs are shown in red, β-OHAAs are shown in blue, and configurations assigned by Inoue are shown in green.

The yaku'amides are attractive synthetic targets due to their striking molecular architecture, potent bioactivity, distinctive mode of action, and natural scarcity. In 2013, Inoue and co-workers constructed both epimers of the initially proposed structure of **1** and assigned the *S*-configuration to the NTA stereocenter.[4] Their subsequent attempts to prepare **2** cast doubt on the originally assigned structures of both yaku'amides. In a painstaking effort involving total synthesis combined with degradation studies conducted on ca. 0.1 mg each of **1** and **2**, Inoue and co-workers confirmed the *S*-stereochemistry of the NTA moiety and determined that the configurational assignments of two pairs of adjacent residues (D- and L-β-OHVal, D- and L-Val) had been transposed (Figure 1).[5a] Their further studies employing fluorescent and biotinylated derivatives of **2** established that this peptide inhibits ATP synthesis and also promotes ATP hydrolysis. This divergent effect on these processes, which are both mediated by the mitochondrial enzyme F_0F_1-ATP synthase, is unprecedented.[5b]

In addition to establishing the structures of **1** and **2** and revealing key aspects of their mode of action, Inoue's pioneering work highlights the difficulties involved in constructing β-*tert*-hydroxy amino acids and unsymmetrical tetrasubstituted ΔAAs. For example, peptide couplings of fragments with *C*-terminal ΔIle residues were plagued by alkene isomerization via an azlactone intermediate unless the neighboring amide was protected.[4] Similar observations were made by Wandless[6] and Joullié[7] while synthesizing the phomopsins, which contain *E*-ΔIle. Moreover, preparation of (2*S*,3*R*)-β-OHIle required a lengthy seven-step sequence from D-Ser.[8] Inoue and co-workers recently disclosed another total synthesis of **2** that was conducted mostly on solid support.[5c] While their new route is higher yielding and contains fewer purification steps than their previous route, it requires solution-phase preparation of three ΔIle-containing subunits that are used in excess to ensure high-yielding couplings to the resin-bound peptide. Prompted by our interest in constructing unusual peptides[9] and devising efficient routes to tetrasubstituted ΔAAs and β-*tert*-hydroxy amino acids, we targeted the yaku'amides for synthesis. Herein, we report a concise and convergent total synthesis of **1** that introduces novel strategies for generating these challenging residues and does not require large excesses of precious intermediates.

Our retrosynthetic analysis of **1** is shown in Scheme 1. Disconnection of the indicated amide bonds revealed three key intermediates: the NTA (**3**), left-hand pentapeptide **4**, and nonapeptide **5**. Following Inoue's precedent,[4,5] we planned to attach the NTA in the final step of the synthesis. Recognizing that *E*- and *Z*-ΔIle would be the most challenging components of **1** to prepare, we divided the rest of the structure into a smaller subunit containing two of these residues (**4**) and a larger subunit possessing only one such residue (**5**). This approach would maximize convergency, as the number of linear steps required to access each intermediate should be comparable. Inspection of **5** indicated that it could be derived from dipeptide **6**, tripeptide **7**, and tetrapeptide **8**. We decided to employ base-free OsO_4-catalyzed aminohydroxylation[10] to construct the β-OHAAs and a

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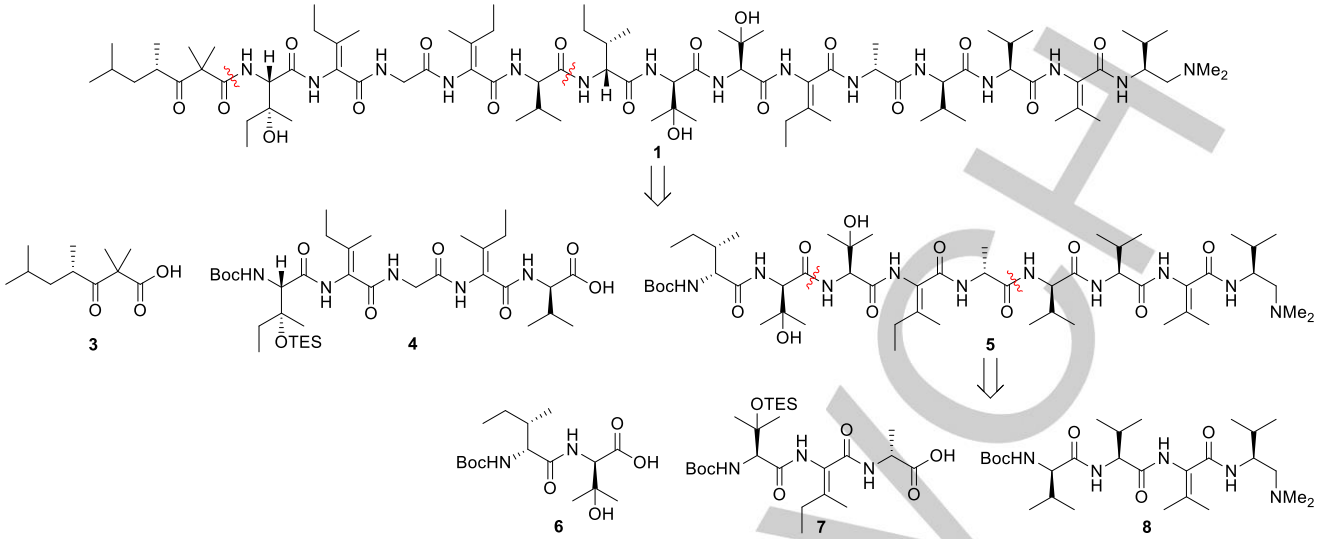
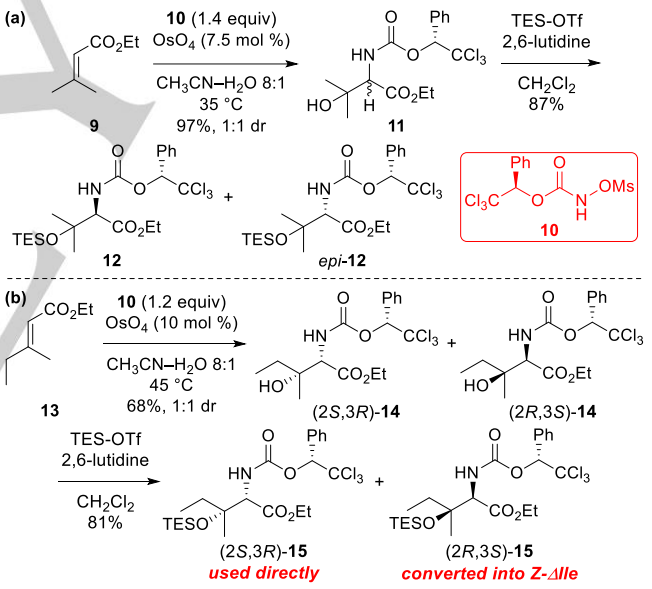


Scheme 1. Retrosynthesis of **1**. Boc = *tert*-butoxycarbonyl, TES = triethylsilyl.

sequence combining aminohydroxylation with stereospecific *anti* dehydration and O→N acyl transfer[11] to install the ΔIle residues without recourse to backbone amide protection.

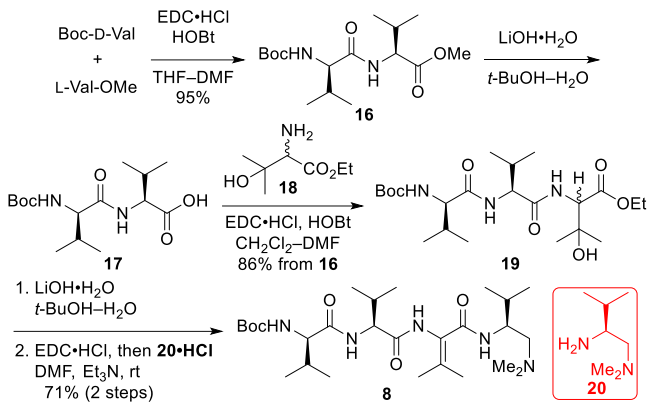
Attempts to develop an enantioselective base-free aminohydroxylation leading to β-OHVal and β-OHIle derivatives were fruitless,[10d] in line with the observations of McLeod and co-workers.[10c] Accordingly, we evaluated chiral nitrogen source reagents. Base-free aminohydroxylation of ethyl 3,3-dimethylacrylate (**9**) with Lebel's mesyloxycarbamate **10**[12] afforded **11** in 97% yield and 1:1 dr (Scheme 2a). Fortunately, the fact that both enantiomers of β-OHVal are present in **1** allowed us to capitalize on this result. Thus, TES protection afforded a separable mixture of D-β-OHVal derivative **12** and L-β-OHVal derivative *epi*-**12** in 87% yield.[13] The generation of these residues simultaneously in just two steps from **9** illustrates the efficiency of the chiral-reagent-based aminohydroxylation strategy. Application of this chemistry to enoate **13** furnished the required β-OHIle derivative (2*S*,3*R*)-**15** along with its separable diastereomer (Scheme 2b).[13] The latter compound was funnelled into the synthesis of **1** via transformation into *Z*-ΔIle precursor **22**,[14] enabling the productive use of both isomers obtained from the aminohydroxylation reaction. The lower yield of **14** compared to **11** presumably reflects the impact of the steric hindrance of the alkene substrate (i.e., **13** vs **9**) on the aminohydroxylation reaction.



Scheme 2. Aminohydroxylation-based synthesis of β-OHAAs present in **1**. Tf = trifluoromethanesulfonyl, Ms = methanesulfonyl.

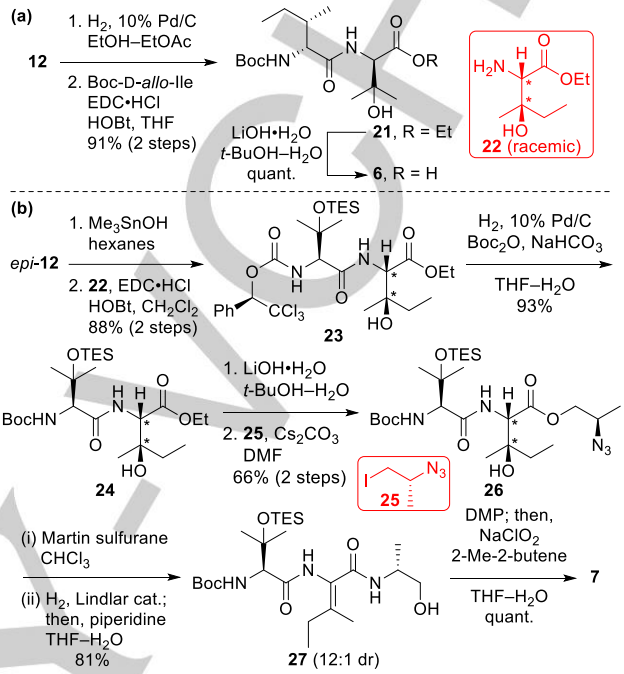
We anticipated that right-hand tetrapeptide **8** would be the simplest of the key subunits of **1** to prepare since it contains ΔVal and not *E*- or *Z*-ΔIle. Indeed, the absence of alkene stereochemistry allowed us to construct **8** rapidly as shown in Scheme 3 by capitalizing on the propensity of peptides with *C*-terminal ΔAAs to form azlactones upon treatment with peptide coupling agents.[4,6,7] First, coupling of Boc-D-Val with L-Val-OMe and subsequent hydrolysis delivered dipeptide **17**. This acid was coupled with racemic β-OHVal derivative **18**[15] to furnish tripeptide **19** as an inconsequential mixture of diastereomers.

Saponification of **19** was followed by treatment of the intermediate acid with EDC•HCl, which served to both activate the carboxylate and dehydrate the tertiary alcohol. This triggered spontaneous formation of an azlactone, which was opened[16] upon addition of amine **20**,[17] generating tetrapeptide **8** in 71% yield from **19**.



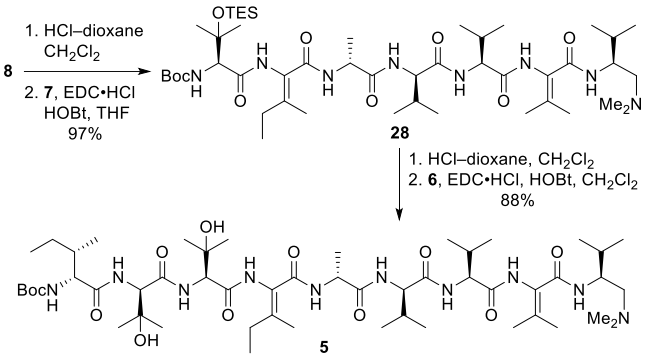
Scheme 3. Synthesis of right-hand tetrapeptide **8**. EDC•HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

Dipeptide **6** and tripeptide **7** were then constructed as outlined in Scheme 4. The chiral carbamate and the TES group were simultaneously removed from **12** via hydrogenolysis in an EtOH–EtOAc solvent mixture, and the resulting amine was coupled with Boc-D-*allo*-Ile to afford dipeptide **21** (Scheme 4a). Saponification furnished acid **6**. Selective cleavage of the ester moiety of *epi*-**12** was challenging due to the base labile nature of the chiral carbamate. We eventually found that Me_3SnOH[18] was suitable for this purpose (Scheme 4b). Coupling of the acid obtained from *epi*-**12** with racemic β-OHIle derivative **22**[11] produced dipeptide **23** as an inconsequential 1:1 mixture of diastereomers. The subsequent hydrolysis and alkylation steps were complicated by the presence of the base-sensitive chiral carbamate. Accordingly, it was exchanged for a more robust Boc group to afford **24** in a single step. The use of $NaHCO_3$ in this reaction was key to preventing TES ether cleavage. Hydrolysis of the ethyl ester of **24** was followed by alkylation with enantiopure iodide **25**,[19] producing β-azidoethyl ester **26** in 66% yield over two steps. A survey of bases in the alkylation revealed that Cs_2CO_3 was most effective at suppressing retroaldol fragmentation of the β-OHIle residue. After some experimentation, we developed a one-pot version of our dehydration/azide reduction/O→N acyl transfer sequence.[11] Thus, treatment of **26** with the Martin sulfurane induced stereoconvergent *anti* dehydration, and a solvent switch set the stage for azide reduction via Lindlar hydrogenation. Addition of piperidine upon completion of the reduction triggered O→N acyl transfer, delivering *Z*-ΔIle-containing tripeptide **27** in 77% yield and 12:1 dr. The trace amounts of *E*-isomer are likely generated during the reduction or the acyl transfer, as no minor isomers were visible in ^{1}H NMR spectra of the crude dehydration product. This one-pot protocol gives slightly better results than our original procedure that employed PMe_3 to reduce the azide.[11] Finally, one-pot Dess–Martin/Pinnick oxidation[20] of **27** with complete removal of the acetic acid byproduct during workup delivered a quantitative yield of acid **7**.



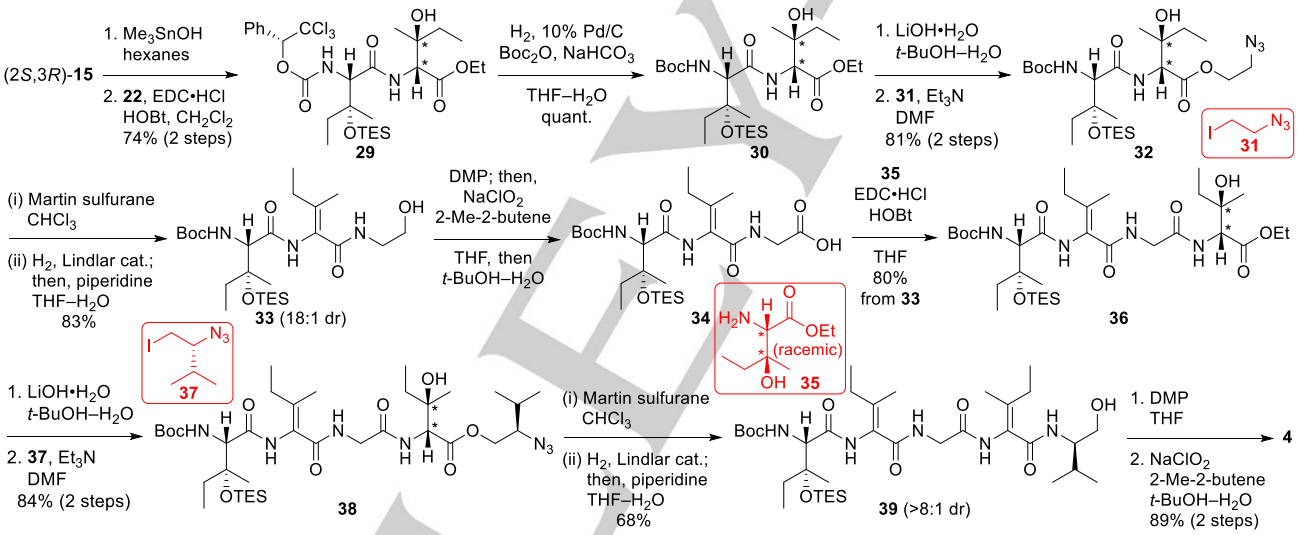
Scheme 4. Syntheses of dipeptide **6** and tripeptide **7**. Stereocenters marked with asterisks show relative, not absolute, stereochemistry. DMP = Dess–Martin periodinane.

Intermediates **6–8** were elaborated into nonapeptide **5** as shown in Scheme 5. First, exposure of right-hand tetrapeptide **8** to HCl removed the Boc moiety, and coupling with tripeptide **7** furnished heptapeptide **28** in excellent yield. Then, treatment of **28** with HCl cleaved the Boc and TES groups simultaneously. Coupling of the crude heptapeptide amine with dipeptide **6** delivered nonapeptide **5** in high yield. Attempted couplings with either or both tertiary alcohols protected were unsuccessful, presumably due to the steric hindrance introduced by the silyl ethers. HPLC analysis of the heptapeptide and the nonapeptide indicated that little if any epimerization occurred during the two fragment couplings.



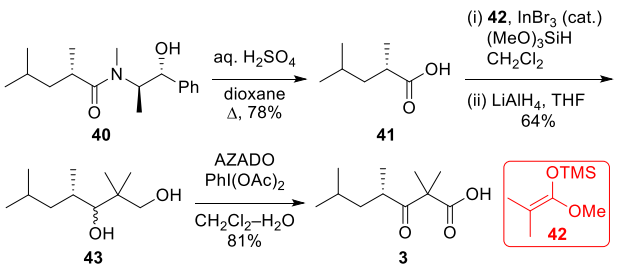
Scheme 5. Synthesis of nonapeptide **5**.

The synthesis of left-hand pentapeptide **4** began with Me_3SnOH-mediated hydrolysis of β-OHIle derivative (2*S*,3*R*)-**15** and coupling of the resulting acid to racemic amine **22**. Dipeptide **29** was obtained in good yield as an inconsequential mixture of diastereomers (Scheme 6). The three-step transformation of **29** into β-azidoethyl ester **32** proceeded similarly to the conversion of **23** into **26** (see Scheme 4b), with the exception that the carboxylate alkylation proceeded best with Et_3N instead of Cs_2CO_3. Gratifyingly, **32** underwent facile stereoconvergent *anti* dehydration followed by azide reduction and O→N acyl transfer, furnishing tripeptide **33** in 83% yield and 18:1 dr. One-pot Dess–Martin/Pinnick oxidation produced acid **34**, which was coupled with racemic β-OHIle derivative **35**[11] (the diastereomer of **22**) to afford tetrapeptide **36**. The familiar three-step sequence of reactions used to convert **36** into alcohol **39** proceeded smoothly in spite of the bulkiness of iodide **37**.[11] Assessment of the diastereomeric ratio of **39** by ^{1}H NMR spectroscopy was complicated by the presence of both *E*- and *Z*-ΔIle in this compound. Nonetheless, it was clear that any alkene isomerization during the azide reduction–O→N acyl transfer process was at most minimal. Sequential oxidation of **39** using the Dess–Martin and Pinnick protocols delivered the key left-hand pentapeptide **4**.



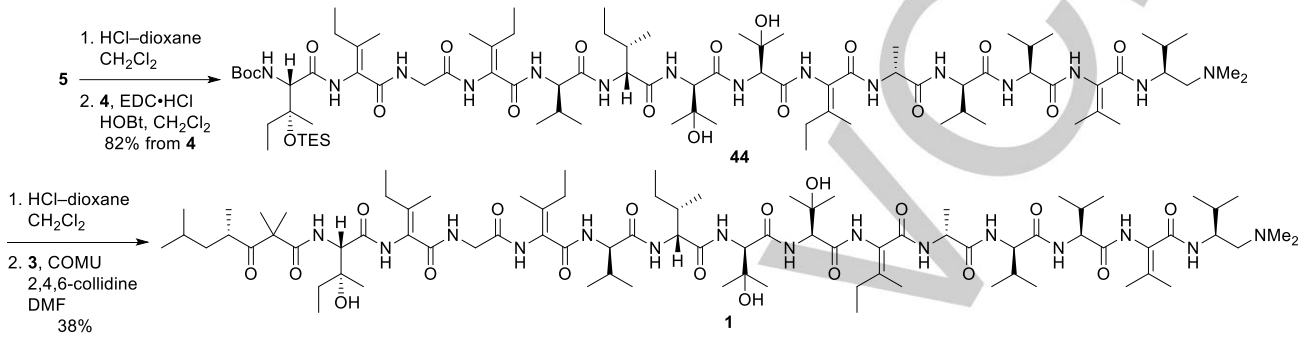
Scheme 6. Synthesis of pentapeptide **4**. Stereocenters marked with asterisks show relative, not absolute, stereochemistry.

The *N*-terminal acyl subunit (NTA) **3** was constructed via the streamlined route depicted in Scheme 7. Acidic hydrolysis[21] of known pseudoephedrine amide **40**[22] furnished enantiopure carboxylic acid **41**. Claisen condensation of **41** and silyl ketene acetal **42** was accomplished using Baba's protocol employing trimethoxysilane and catalytic $InBr_3$.[23] *In situ* reduction of the resulting β-keto ester by addition of $LiAlH_4$ yielded diol **43** as an inconsequential mixture of diastereomers. Oxidation of **43** to β-keto acid **3** was achieved by slightly modifying the procedure described by Inoue[4] that enlists AZADO and $PhI(OAc)_2$.[24] Our route to **3** (three steps from **40** and five steps from commercially available compounds)[25] is significantly shorter than the previously published ten-step synthesis of this compound.[4]



Scheme 7. Synthesis of NTA carboxylic acid **3**. AZADO = 2-azaadamantane *N*-oxyl, TMS = trimethylsilyl.

The three building blocks **3–5** were assembled and elaborated into **1** as outlined in Scheme 8. HCl-mediated Boc-deprotection of nonapeptide **5** set the stage for the critical coupling with pentapeptide **4**. Extensive experimentation revealed that the combination of EDC•HCl and HOBt with CH_2Cl_2 as solvent was uniquely effective for joining these complex building blocks. Other conditions delivered inferior results. One-step deprotection of the Boc and TES groups from tetradecapeptide **44** was facile in the presence of HCl, and attachment of carboxylic acid **3** to the resulting amine was achieved by following the precedent developed by Inoue and co-workers.[4] HPLC has been established as the most reliable technique for distinguishing yaku'amide A from its isomers.[5] Accordingly, we were pleased to find that our synthetic sample of **1** was identical by HPLC to a synthetic sample from the Inoue laboratory that was previously demonstrated to be identical to naturally occurring **1**.



Scheme 8. Completion of the total synthesis of **1**. COMU = 1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate.

In summary, we have synthesized the unusual peptide natural product yaku'amide A. Its β-*tert* hydroxy amino acids were rapidly constructed via regioselective aminohydroxylation of enoates enlisting a chiral mesyloxycarbamate. Stereospecific preparation of the *E*- and *Z*-ΔIle residues was accomplished by means of an *anti* dehydration utilizing the Martin sulfurane. The dehydration was merged with an azide reduction and an O→N acyl transfer into a one-pot process. This streamlined procedure enabled the generation of *E*- and *Z*-ΔIle and couplings at their *C*-termini to proceed in a single step with only negligible amounts of alkene isomerization. These methods facilitated a convergent synthetic route to **1** (19-step longest linear sequence with 13 chromatographic purifications, 3.5% overall yield) that compares favorably to Inoue's pioneering synthesis of this compound (25-step longest linear sequence, 1.9% overall yield).[4,5a] The use of straightforward protocols combined with the lack of reagents that are difficult to handle bodes well for the scalability of our route. Although Inoue's solid-phase synthesis of **2** possesses some advantages such as a higher yield (9.1%) and fewer required purifications,[5c] it also has some intrinsic limitations. For example, the requirement for large excesses of precious intermediates that are challenging to construct attenuates the benefit offered by the high overall yield.[26] Perhaps more significant is the fact that solid-phase peptide synthesis requires a linear rather than convergent synthetic strategy. Our route complements Inoue's work by avoiding excess amounts of valuable subunits and by proceeding in a convergent fashion. The latter feature should prove highly advantageous in the construction of yaku'amide A analogs. Specifically, the preparation of a few variants of each key subunit in our route followed by their convergent assembly would afford numerous analogs, thereby constituting a notable application of the "Multiplication of Diversity" strategy.[27] Accordingly, the synthesis and biological evaluation of analogs of **1** will be the subject of future reports from our laboratory.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: peptides • natural products • total synthesis • aminohydroxylation • O→N acyl transfer

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[13] Details of the assignments of the absolute configurations of **12**, *epi*-**12**, (2*S*,3*R*)-**15**, and (2*R*,3*S*)-**15** are found in the Supporting Information.

[14] Please see the Supporting Information for details.

[15] Amine **18** was prepared by a modification of the procedure used in ref. 10b to prepare this compound (see Supporting Information for details).

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[19] Details of the synthesis of **25** are found in the Supporting Information.

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[25] The success of the oxidation of **43** is dependent on the availability and quality of AZADO, which is expensive and often out of stock in the USA. While it can be synthesized, characterization is challenging due to its radical nature. Accordingly, we developed an alternate route to **3** that does not rely on AZADO. Details are found in the Supporting Information.

[26] Shortly before this manuscript was submitted, Inoue and co-workers reported a second-generation solid-phase synthesis of yaku'amide B: K. Kamiya, K. Miura, H. Itoh, M. Inoue, *Chem. Eur. J.* 10.1002/chem.202003858. While this new route improves upon the first-generation synthesis published in ref 5c, it still requires excess amounts of alkenyl azides and air-sensitive phosphinophenol esters, both of which must be synthesized in solution.

[27] (a) D. L. Boger, W. Chai, Q. Jin, *J. Am. Chem. Soc.* **1998**, *120*, 7220. (b) D. L. Boger, W. Chai, *Tetrahedron* **1998**, *54*, 3955. (c) D. L. Boger, W. Jiang, J. Goldberg, *J. Org. Chem.* **1999**, *64*, 7094.

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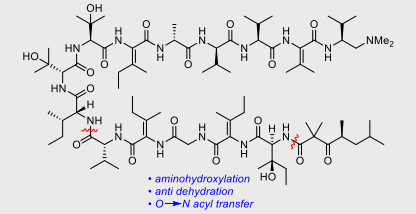
Layout 1:

COMMUNICATION

Yaku'amide A, an anticancer peptide, was synthesized via a route featuring a one-pot *anti* dehydration–azide reduction–O→N acyl transfer process for stereospecific construction of *E*- and *Z*-ΔIle. OsO_4-catalyzed aminohydroxylation was employed to produce the β-hydroxy amino acids.



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Convergent Total Synthesis of Yaku'amide A