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Direct Imine Acylation: Synthesis of the Proposed Structures of ‘Upenamide

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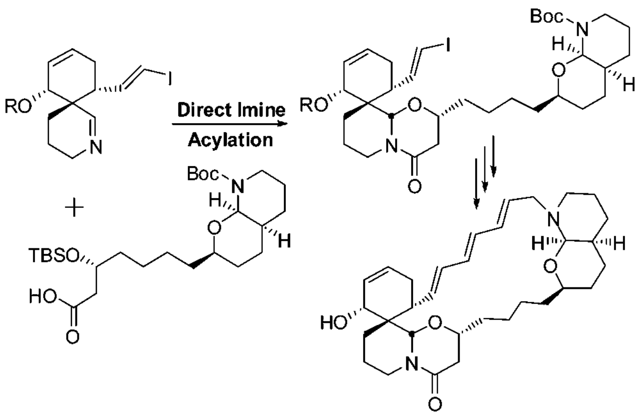
ABSTRACT



The synthesis of the two proposed structures of macrocyclic marine natural product ‘upenamide is reported. The key step utilizes direct imine acylation (DIA) with a protected β-hydroxy acid to construct the key tricyclic ABC ring system. The macrocyclization was completed in the final step using a Stille cross-coupling reaction.

The macrocyclic diamine alkaloid ‘upenamide, isolated from the Indonesian sponge *Echinochalina sp*., was reported in 2000 by Scheuer et al., with its unusual name derived from the Hawaiian word ‘upena, meaning fishing net or trap.[1] The absolute stereochemistry of the novel tricyclic spirooxaquinolizidinone ABC ring system was assigned following a series of NMR experiments, but only the relative stereochemistry of the unusual octahydropyrano[2,3-b]pyridine DE ring system has been confirmed, and it was assumed that the synthesis of both diastereoisomers **1a** and **1b** was needed to confirm the structure of the natural product. No biological activity was found, but bioassays were limited because of the scarcity of the natural material, necessitating synthesis to further probe its biological properties. The total synthesis of ‘upenamide has not been reported, with synthetic efforts to date focusing on the synthesis of the two polycyclic core units.[2]

The retrosynthetic strategy was based on a late stage palladium-catalyzed cross-coupling to perform the macrocyclization, with the requisite diene component installed via *N*-alkylation with a functionalized diene (**2**) (Figure 1). Our key step relies on the application of the direct imine acylation methodology (DIA) described in the preceding communication to install the A-ring.[3] It was anticipated that the coupling of an imine of the form **4** with a carboxylic acid derivative bearing a protected alcohol (**5**) would form an *N*-acyliminium ion, which upon protecting group cleavage, would cyclize to form the A-ring and complete the ABC portion of ‘upenamide. A TBS-group

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(1) Jiménez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelley, M. *J. Org. Chem.* **2000**, *65*, 8465.

(2) (a) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181. (b) Mons, S.; Malves Maia, A.; Mons, S.; Pereira de Freitas Gil, R.; Marazano, C. *Eur. J. Org. Chem.* **2004**, 1057. (c) Kiewel, K.; Luo, Z.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 5163. (d) Han., J. L.; Ong, C. W. *Tetrahedron* **2007**, *63*, 609. (e) Cayley, A. N.; Cox., R. J.; Ménard-Moyon, C.; Schmidt, J. P.; Taylor, R. J. K. *Tetrahedron Lett.* **2007**, *48*, 6556. (f) Ménard-Moyon, C.; R. J. K. *Eur. J. Org. Chem.* **2007**, 3698. (g) Schmidt, J. P.; Beltran-Rodil, S.; Cox, R. J.; Mcallister, G. D.; Reid., M.; Taylor, R. J. K. *Org. Lett.* **2007**, *20*, 4041. (h) Luo, Z.; Peplowski, K.; Sulikowski, G. A. *Org. Lett.* **2007**, *9*, 5051.

(3) Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. *Org. Lett.* **2012**, dx.doi.org/10.1021/ol303073b.

10.1021/ol3030764

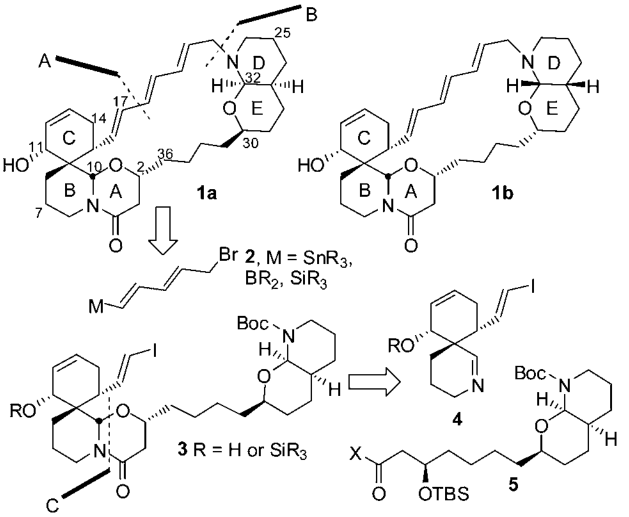
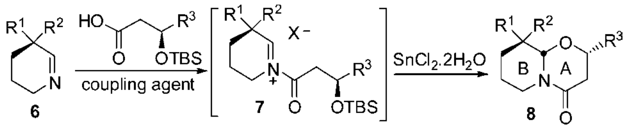


Figure 1. Retrosynthesis. (A) Palladium-catalyzed cross-coupling. (B) Boc cleavage and then *N*-alkylation. (C) See Scheme 1.

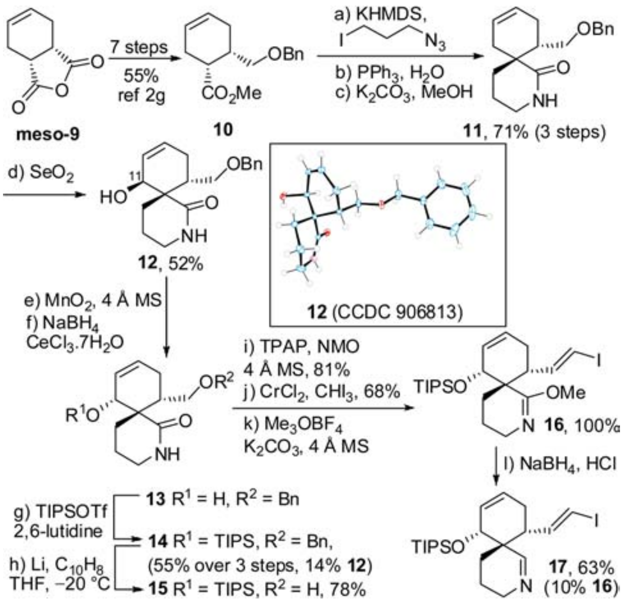
was chosen to protect the alcohol in **4**, as we predicted that $SnCl_2 \cdot 2H_2O$ could be used to effect its cleavage and promote the cyclization in one pot (Scheme 1).[4] This approach offers a significant advantage over our previous synthesis of the ABC tricycle: DIA replaces three discrete steps and has the advantage of incorporating the DE ring system in the coupling partner, completing the first synthesis of a species containing all of the rings A–E.

Scheme 1. Direct Imine Acylation (DIA)



The synthesis of the BC ring fragment **17** began with the conversion of *meso*-anhydride **9** into enantioenriched ester **10** (94% *ee*), via a seven step sequence as described in our previous report.[2g] Alkylation with 1-azido-3-iodopropane,[5] was followed by Staudinger reduction and reaction with aqueous K_2CO_3 to generate lactam **11**. The introduction of the key C-11 allylic oxygen was effected using a SeO_2 oxidation,[2g] affording **12** as a single isomer; the regio- and stereoselectivity of this process was confirmed by obtaining the X-ray crystal structure of **12**.[6] This compound had the desired regiochemistry but the incorrect stereochemistry, requiring that the C-11 stereocenter be inverted. This was achieved via oxidation with MnO_2, followed by Luche reduction[7] to give a roughly 10:1 mixture of pseudoequatorial alcohol **13**,[8] along with a small amount of returned **12**. Conveniently, the treatment of this mixture with triisopropylsilyl triflate resulted in the protection of **13** as silyl ether **14**, while the undesired epimer **12** was inert under these conditions and so was readily separated by column chromatography and recycled. Benzyl cleavage was achieved in good yield using lithium naphthalenide, and the resulting alcohol **15** was oxidized via a Ley–Griffith oxidation,[9] converted into a vinyl iodide by a Takai olefination[10] and treated with Meerwein's salt to form imidate **16**. The synthesis of imine **17** was completed by partial reduction with $NaBH_4$, catalyzed by the dropwise addition of HCl (Scheme 2).

Scheme 2. Synthesis of BC Coupling Partner **17**



Attention turned to the synthesis of the DE ring-containing compound **25a**. Enantioenriched propargylic alcohol **19a** was formed in 93:7 *er* via reduction of ketone **18** with *R*-Alpine Borane.[2c,11] Meanwhile, protected piperidinone **20** was converted into vinyl triflate **21**,[12] which was formed along with its regioisomer and was obtained cleanly following column chromatography. The Sonogashira coupling of **21** with **19a** proceeded smoothly and was followed by selective alkyne hydrogenation, as demostrated by Sulikowski,[2c] before the DE ring system was completed by acid-catalyzed cyclization using an excess of $SnCl_2 \cdot 2H_2O$, affording the *N*,*O*-acetal **23a** in good overall yield. These conditions have been successfully employed in

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[4] Cayley., A. N.; Gallagher, K. A.; Ménard-Moyon, C.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Synthesis* **2008**, 3846.

[5] Yao, L.; Smith, B. T.; Aube, J. *J. Org. Chem.* **2004**, *69*, 1720.

[6] CCDC 906813. See Supporting Information for a larger ORTEP image.

[7] Gemal, A. L.; Luche, J. -L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

[8] The C-11 stereochemsitry is supported by its ^{13}C NMR chemical shift, as demonstrated in reference 2g.

[9] Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625.

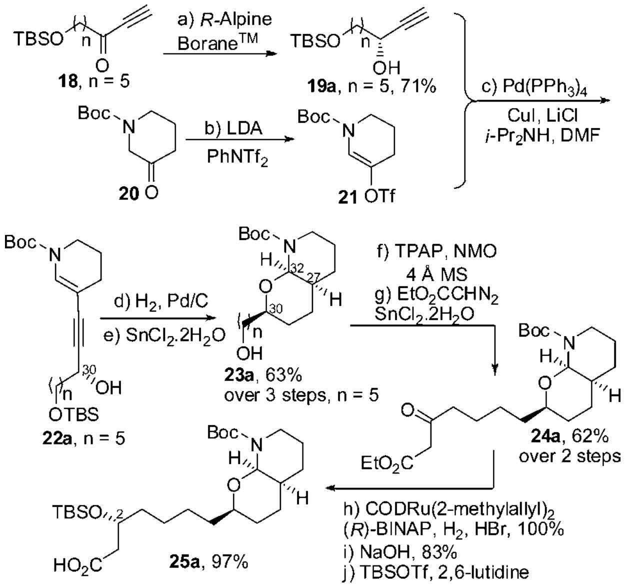
[10] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

[11] 93:7 *er* verified by chiral HPLC of benzoate ester of **19a** (see Supporting Information)

[12] Vicart, N.; Cazes, B.; Gore, J. *Tetrahedron* **1996**, *52*, 9101.

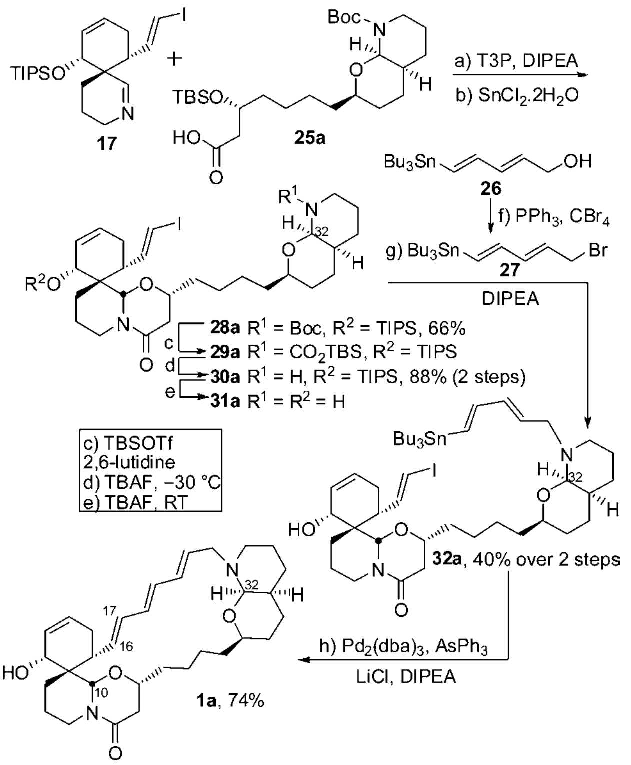
related cyclizations by our group and had the additional advantage of promoting concomitant desilylation of the remote primary alcohol.[4] As found previously, the C-30 alcohol stereocenter controlled the relative stereochemistry of the two new stereocenters (C-27 and C-32) at the DE ring junction, affording a *cis*-fused ring system, which was assigned on the basis of the small coupling constant and high chemical shift of H-32.[2c] Further elaboration by Ley–Griffith oxidation[8] and Roskamp reaction[13] afforded 1,3-dicarbonyl compound **24a**. Asymmetric reduction using a modified Noyori reduction[14] installed the C-2 stereocenter with excellent stereocontrol (99:1 ratio at this stereocenter, verified by HPLC, see Supporting Information), and the synthesis of DIA coupling partner **25a** was completed by TBS-protection and hydrolysis.

Scheme 3. Synthesis of the DE Ring System **25a**



The scene was set to attempt the key DIA reaction. Imine **17** and acid **25a** were treated with peptide coupling reagent T3P[15] and Hünig's base at room temperature in THF. This resulted in the consumption of both starting materials, affording a mixture of products, including a small amount of **28a**. No attempt was made to purify the components of this mixture, however, as direct treatment with excess $SnCl_2 \cdot 2H_2O$ in DCM resulted in deprotection and a smooth progression to the desired tricyclic spirooxaquinolizidinone **28a**. Crucially, the ABC ring system of **28a** was formed in a > 10:1 mixture of diastereoisomers, with the major diastereoisomer isolable cleanly following column chromatography.[16] The major diastereoisomer is thought to be that shown with *N*,*O*-acetal proton H-10 being *syn* to H-2 in line with previous work in our group.[2g] Its high downfield ^{1}H NMR shift (δ 5.27) and opposite upfield ^{13}C NMR shift for C-10 (δ 81.4) are characterisic, and the absence of Bohlmann bands[17] in its IR spectra provides evidence for this, in accord with the data and rationale in the 'upenamide isolation paper.[1]

Scheme 4. Completion of the Synthesis of **1a**



Cleavage of the Boc protecting group was achieved using a two step sequence by first converting **28a** into TBS-carbamate **29a** followed by treatment with TBAF, affording **30a**.[2c] The need to employ these unusually elaborate deprotection conditions is due to the fact that **30a** is unstable and prone to epimerization at C-32.[18] Treatment with more TBAF, this time to cleave the TIPS protecting group, revealed **31a**, which was used immediately in the subsequent *N*-alkylation without purification. This was achieved by heating **31a** at reflux with Hünig's base and stannylpentadienyl bromide **27**, itself prepared in situ from known alcohol **26**,[19] affording key macrocyclization precursor **32a**. Finally, to promote the desired intramolecular Stille coupling, the reaction was performed under high dilution conditions (2 mM), using Pd_2dba_3, $AsPh_3$, LiCl

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(13) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

(14) Genêt, J. P.; Ratovelomanana-Vidal, M. C.; Cano de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801.

(15) Wissmann, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed.* **1980**, *19*, 133.

(16) Note that the DE ring system still exists as a 93:7 mixture of diastereoisomers, but that these are indistiguishable by NMR spectroscopy.

(17) Bohlman, F. *Angew. Chem.* **1957**, *69*, 641.

(18) Indeed **30a** and all subsequent products in which the ring-D-nitrogen protecting group is not present are similarly unstable, particularly with respect to acid. This necessitated the use of triethylamine as a coeluent in the chromatography of these substrates.

(19) Matsushita, N.; Matsuo, Y.; Tsuchikawa, H.; Matsumori, N.; Murata, M.; Oishi, T. *Chem. Lett.* **2009**, *38*, 114.

and Hünig's base in THF. After stirring for 1 h at room temperature, the reaction mixture was analyzed by high resolution ESI$^+$ mass spectrometry, and we were delighted to observe a major signal consistent with 'upenamide[20] and only trace amounts of the starting material. Following standard workup and column chromatography, the desired macrocycle **1a** was isolated in 74% yield as a white amorphous solid.

Unfortunately a direct comparison between the spectroscopic data of **1a** and natural 'upenamide could not be made, given that **1a** is insoluble in CD_3OD, the NMR solvent used to characterize 'upenamide by the isolation chemists. Its NMR data was instead measured in $CDCl_3$ and showed considerable differences to that of the natural product, which allied to its solubility properties, makes it likely that **1a** is not 'upenamide.[21]

Aside from these comparisons, all of the spectroscopic data accrued for **1a** supports its structural assignment as being that shown. The methods described above that were used to confirm the stereochemsitry of each of the 8 stereogenic centers in its precursors all continue to apply throughout the synthesis, and crucially in **1a**, suggesting that any unexpected epimerization is unlikely. Evidence for the geometry of the C-16/C-17 alkene can be found in the ^{1}H NMR spectra, as H-16 appears as a discrete signal with a large coupling constant typical of an *E*-alkene.[22] Unfortunately the geometry of remaining two alkenes of the triene could not be directly observed because of the overlap of signals, although all of the corresponding protons in its precursor **32a** were clearly visible, supporting the all-*trans*-assignment.[23]

The synthesis of the other proposed structure **1b** (Figure 1) was therefore completed using the same route described above, but using *S*-Alpine Borane to generate **19b**, the epimer of alcohol **19a** (Schemes 3 and 4). The synthesis proceeded similarly well, with the spectroscopic data of the diastereomeric precursors **25b** and **28b**–**32b** all very similar to those of **25a** and **28a**–**32a**. The Stille macrocyclization was performed under the same conditions, affording macrocycle **1b** as a colorless oil, albeit contaminated by two minor diastereoisomers, which most likely arise from epimerization of the *N*,*O*-acetal stereogenic centers C-10 and C-32, and a small amount of $AsPh_3$. In this instance the product was soluble in CD_3OD enabling a direct comparison with natural 'upenamide to be made, but unfortunately, the NMR data were significantly different to those of the natural compound for each of the three compounds in this mixture (see Supporting Information).

Thus, the NMR data of both **1a** and **1b** does not match that reported for 'upenamide, suggesting that neither is the natural product.[24] It is regrettable that neither synthetic structure could be unambiguously verified by X-ray crystallography, but as both compounds are highly unstable and degrade quickly in solution,[25] this was not possible, despite considerable effort. We therefore cannot state categorically that 'upenamide has been misassigned, but at the very least, this work means that the proposed structures of 'upenamide should be treated with caution and that a structural re-evaluation may be required.

In summary, we have completed the synthesis of the two proposed structures of 'upenamide **1a** and **1b**. Noteworthy steps include the DIA reaction used to install the A ring, a 20-membered ring Stille macrocyclization and each of the two $SnCl_2 \cdot 2H_2O$-mediated stereocontrolled *N*,*O*-acetal formations. Future work will focus on establishing unambiguously the structures of macrocycles **1a** and **1b** before, if necessary, seeking to re-evaluate the structure of 'upenamide through total synthesis.

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Supporting Information Available. Synthetic procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[20] Found MH$^+$ 523.3521, $C_{32}H_{47}N_2O_4^+$ requires 523.3530.

[21] We wish to thank Mr. Wesley Yoshida, the only author of the 'upenamide isolation paper (ref 1) remaining at the University of Hawaii, for his attempts to find a sample of natural 'upenamide or any NMR data recorded in $CDCl_3$. Unfortunately neither could be found.

[22] δ_H 6.31 (1H, dd, J = 14.4, 10.3, H-16)

[23] $J_{(16-17)} = 14.3$ Hz, $J_{(18-19)} = 18.8$ Hz, $J_{(20-21)} = 15.0$ Hz.

[24] It was considered that amine salt formation may account for the differences in NMR data; however, while the addition of TFA to each of **1a** and **1b** led to a change in their NMR spectra, neither accorded with natural 'upenamide, and product decomposition was clearly evident.

[25] Within a few hours of standing in $CDCl_3$, a clean sample of **1a** contained additional signals in its ^{1}H NMR spectrum, thought to arise from C-10 and/or C-32 epimerization. After 1 week in DCM/hexane (attempted crystallization), complete degradation was observed.