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Formation of the BC Ring System of Upenamide via a Staudinger/aza-Wittig Reaction

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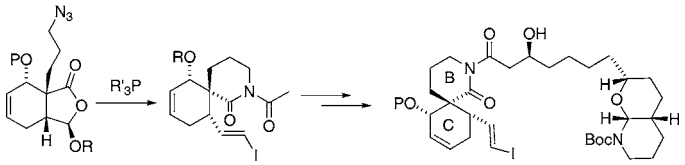
ABSTRACT



The BC ring system of upenamide was assembled using a stereoselective Diels–Alder reaction followed by a Staudinger/aza-Wittig/imine hydrolysis reaction. Stereoselective aldol coupling with an aldehyde that incorporates the DE ring system led to an advanced synthetic intermediate en route to the marine alkaloid upenamide.

Upenamide, a unique macrocyclic alkaloid, was isolated from the crude extract of the marine sponge *Echinochalina* collected from Derawan Island in Indonesia, as reported by Scheuer in 2000.[1] Structurally, upenamide features an unsaturated 20-membered macrocycle interconnecting spirooxaquinolizidinone and hemiaminal ring systems, likely derived from a reduced bis-3-alkylpyridine macrocycle according to the biogenesis of related marine alkaloids such as the xestospongins, manzamines, and saraines.[2] The structure of (−)-upenamide was elucidated primarily by a series of NMR experiments. While the absolute configuration of the spirooxaquinolizidinone substructure was assigned by NMR analysis of the *S*- and *R*-Mosher esters derived at the C11 hydroxyl group,[3] the absolute stereochemistry of the bicyclic hemiaminal ring system was left unassigned. Thus, the structural information currently available is in agreement with the 27*R*, 30*S*, 32*S* or 27*S*, 30*R*, 32*R* isomers (Figure 1). One approach to distinguishing between these two structures is by enantioselective total synthesis of upenamide and correlation with natural (−)-upenamide.

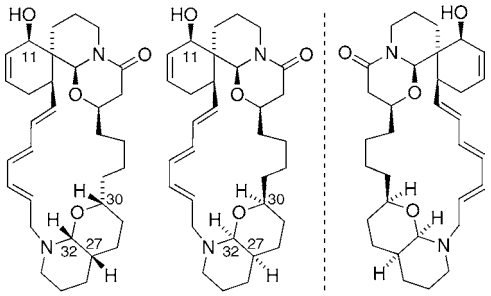


Figure 1. Possible upenamide structures.

In bioassays, upenamide did not show cell growth inhibition against P388, A549, and HT29 cancer cell lines. Further biological evaluation has not been reported perhaps due to insufficient quantities of upenamide. Since sponge collection

(1) Jimenez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelly, M. *J. Org. Chem.* **2000**, *65*, 8465−8469.

(2) (a) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059−2062. (b) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765−794. (c) Guo, Y. W.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **1996**, *52*, 8341−8348. (d) Cutignano, A.; Tramice, A.; De Caro, S.; Villani, G.; Cimino, G.; Fontana, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2633−2636.

(3) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374.

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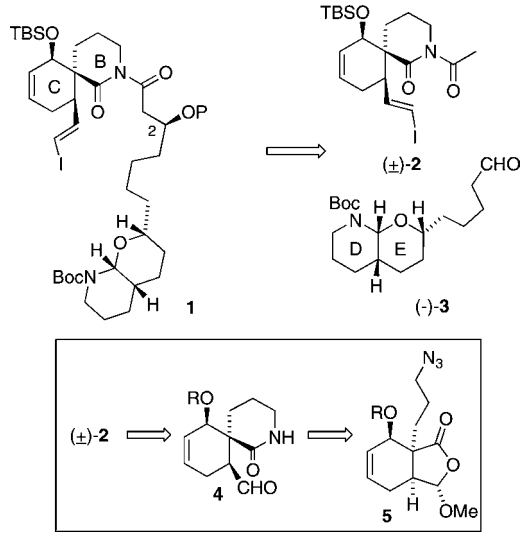
from the Derawan Island is now strongly restricted, it is doubtful the current supply of upenamide will be increased by isolation, leaving total synthesis as the only viable material supplement.[4]

As a means of full stereochemical assignment of (−)-upenamide, our synthetic strategy required delivery of 27*R*,30*S*,32*S*-upenamide and the mirror image of the corresponding 27*S*,30*R*,32*R*-isomer (Figure 1) by stereoselective aldol coupling of racemic (±)-**2** and (−)-**3** followed by the eventual completion of the upenamide ring system (Scheme 1). *This synthetic assembly, in principle, provides sufficient*

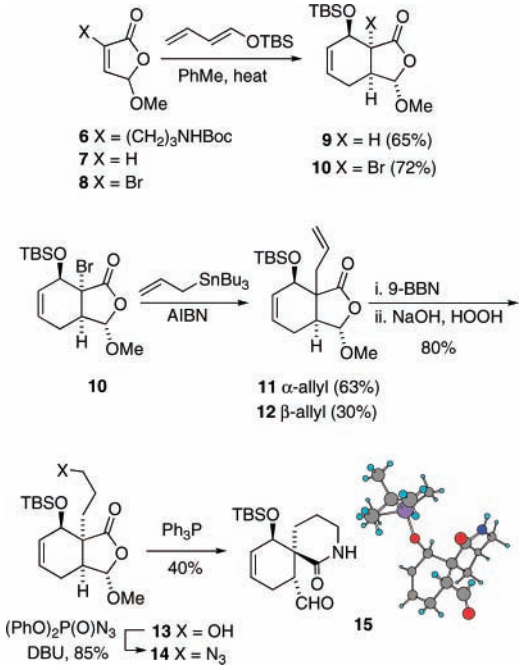
Scheme 1



stereochemical information to unambiguously assign the structure of (−)-upenamide by spectral and optical properties comparison to natural material. Earlier we described a stereocontrolled synthesis of (−)-**3**.[4c] Herein we describe a racemic synthesis of the BC spirocyclic imide (±)-**2** and stereoselective aldol reaction with aldehyde (−)-**3** to deliver the advanced synthetic intermediate **1** and its isomer (not shown).

The preparation of the spirocyclic ring system (±)-**2** presents a significant synthetic challenge due to the required control of three contiguous stereocenters including a central quaternary carbon.[5] A logical precursor to (±)-**2** is aldehyde **4** which we anticipated could be produced by a reductive cyclization of azido lactone **5**, a bicyclic ring system derived from a Diels−Alder reaction (Scheme 1). Feringa has investigated the Diels−Alder reaction of γ-alkoxybutenolides; however, only an intramolecular example has examined the effect of an α-alkyl group on the reactivity and stereoselectivity of this class of dienophiles.[6] Under thermal conditions, no reaction was observed between 1-*tert*-butyldimethylsiloxybutadiene and butenolide **6** (Scheme 2).[7]

Scheme 2



In contrast, the unsubstituted γ-methoxybutenolide **7** readily underwent a Diels−Alder reaction with the same diene to give cycloadduct **9**, albeit with 4:1 endo/exo selectivity. By way of contrast, when 2-bromobutenolide **8** was heated at reflux in toluene with 1-*tert*-butyldimethylsiloxybutadiene, the endo adduct **10** was isolated exclusively as a white crystalline solid.[8] Subsequently, the bromo group located at the ring fusion allowed introduction of a three-carbon fragment by way of a Keck allylation. Unfortunately, the selectivity of the radical-mediated allylation was modest, affording a chromatographically separable mixture of cis (**11**) and trans (**12**) fused isomers resulting in 63 and 30% yield, respectively. The cis isomer (**11**) was then subjected to a hydroboration−oxidation sequence to afford alcohol **13** in 80% yield. Substitution of the hydroxyl group with an azido group was accomplished using diphenylphosphoryl azide and base (DBU)[9] to set the stage for the key Staudinger/aza-Wittig reaction.[10] To this end, azide **14** was heated in toluene

(4) For earlier synthetic work on upenamide, see: (a) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181−4183. (b) Maia, A. A.; Mons, S.; Gil, R. P. D.; Marazano, C. *Eur. J. Org. Chem.* **2004**, 1057−1062. (c) Kiewel, K.; Luo, Z. S.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 5163−5165. (d) Ménard-Moyon, C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2007**, 3698−3704. (e) Schmidt, J. P.; Beltrán-Rodil, S.; Cox, R. J.; McAllister, G. D.; Reid, M.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 4041−4044.

(5) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146.

(6) (a) Feringa, B. L.; Dejong, J. C. *J. Org. Chem.* **1988**, *53*, 1125−1127. (b) Jauch, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2764−2765.

(7) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743−8744.

(8) Maestro, M. C.; Barquilla, M. C.; Martin, M. R. *Tetrahedron: Asymmetry* **1999**, *10*, 3593−3599.

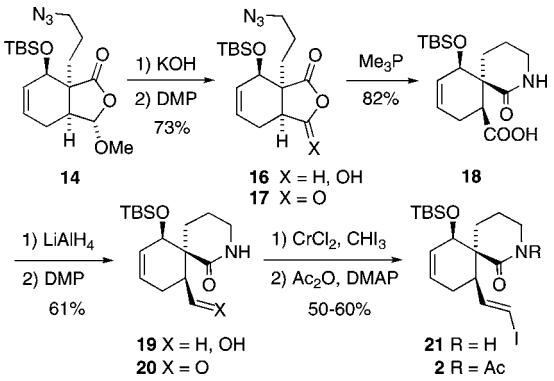
(9) Thompson, A. S.; Humphrey, G. R.; Demarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886−5888.

(10) (a) Jiang, B.; Yang, C. G.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1396−1398. (b) Neubert, B. J.; Snider, B. B. *Org. Lett.* **2003**, *5*, 765−768. (c) Wang, J.; Sakamoto, S.; Kamada, K.; Nitta, A.; Noda, T.; Oguri, H.; Hirama, M. *Synlett* **2003**, 891−893.

at reflux with a slight excess of triphenylphosphine. Following consumption of **14**, as determined by TLC analysis, the reaction was quenched with water. Under these conditions, the major product proved to be aldehyde **15**, the *epimer* of the desired aldehyde (**4**) as determined by single-crystal X-ray analysis. Examination of a representation of the X-ray structure (**15**) shows epimerization relieved an unfavorable 1,3-diaxial interaction with the TBS ether group.

We reasoned that, in contrast to an aldehyde, a carboxylic acid would be far less prone to epimerization. For this reason, we examined the reductive cyclization of anhydride **17** (Scheme 3), derived from methyl acetal **14** in two steps. A

Scheme 3

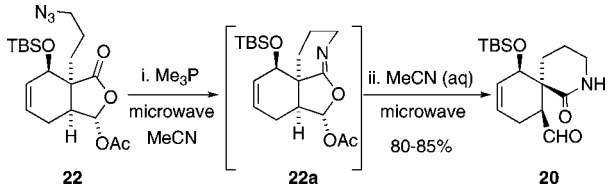


solution of anhydride **17** was stirred at room temperature with a slight excess of trimethylphosphine to afford carboxylic acid **18** as a single isomer. Reduction of **18** with $LiAlH_4$ followed by oxidation with Dess−Martin periodinane gave aldehyde **20** without any epimeric product (**15**) observed. Takai olefination ($CrCl_2$, CHI_3) of **20** gave vinyl iodide **21**, and after N-acetylation, spirocyclic imide **2** was obtained.

While this route delivered the BC spirocyclic ring system (**2**), it was somewhat cumbersome, as it required manipulation of the oxidation state of the carboxaldehyde group. We reasoned that epimerization of aldehyde **20** to **15** was promoted by methoxide ion produced in the course of the Staudinger/aza-Wittig/ imine hydrolysis sequence. In order to avoid production of this moderately strong base, we chose to examine the cyclization of acetate **22**[11] (Scheme 4). After screening various reaction conditions, we determined conversion of **22** to aldehyde **20** via imine **22a**[12] was effected by microwave (20 W, 60 °C) irradiation for 5 min. Introduction of water and further irradiation for 10 min thereafter provided **20** in 80−85% yield with minimal epimerization (**20**/**15**, 10:1).

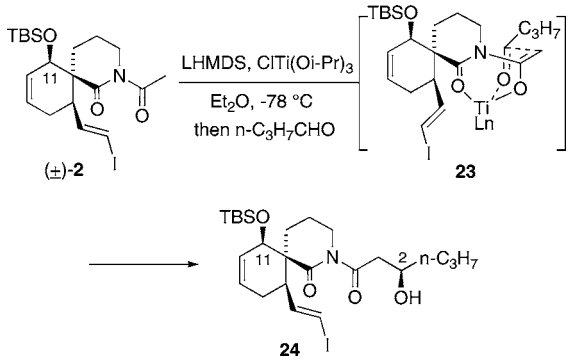
A key consideration in the proposed aldol coupling of imide (±)-**2** and aldehyde (−)-**3** to provide **1** was the

Scheme 4



stereoselectivity of the aldol reaction (vis-à-vis control of the C2 configuration) relative to the chirality harbored within the enolate derived from imide (±)-**2**. In this way, a stereoselective aldol in the correct sense would fashion four of the five stereocenters of the complex spirooxaquinolizidinone ring system of upenamide. After examining various metal enolates (including lithium and boron), it was determined that the titanium enolate derived from (±)-**2** condensed with *n*-butyraldehyde to provide one major aldol isomer (dr 20:1) in 75% yield. The reaction, which utilized an excess of titanium(IV), was proposed to proceed by way of chelate transition state **23** (Scheme 5), whereby the

Scheme 5



aldehyde approaches the titanium enolate from the diastereotopic face opposite the sterically cumbersome TBS group.[13] *The configuration of the C2 secondary alcohol of* ***24*** *has been tentatively assigned based on the transition state model* ***23***.

Under identical reaction conditions, 3.7 equiv of imide (±)-**2** underwent an aldol reaction with aldehyde (−)-**3** to give two inseparable isomers (Scheme 6) in 95% yield. No other isomers were observed within detection limits of ^1H and ^{13}C NMR.

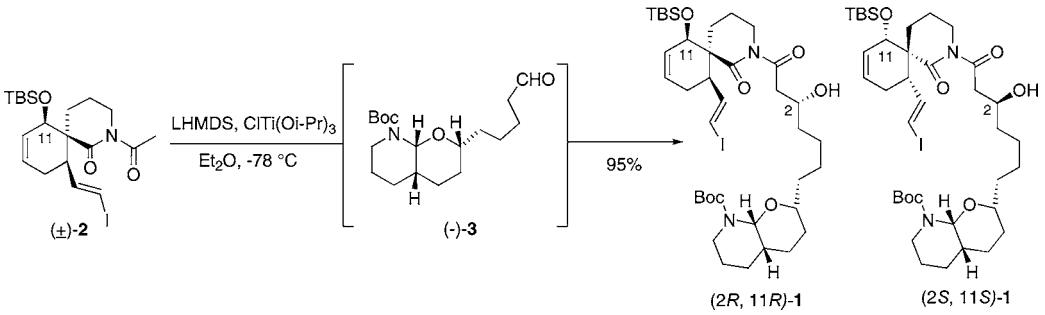
In summary, we have developed a stereocontrolled assembly of the complex spirocyclic ring system embedded in the marine alkaloid upenamide. In addition, we have developed reaction conditions that serve to merge spirocyclic imide (±)-**2** with aldehyde (−)-**3**, and in the process, we have controlled the C2 configuration of upenamide. Remaining synthetic challenges to be addressed in advancing

(11) Acetate **22** was prepared from methyl acetal **14** in two steps: (i) 1 M KOH, 18-crown-6, dioxane, 50 °C; (ii) Ac_2O, DMAP, pyridine, CH_2Cl_2.

(12) Compound **22a** has only been isolated and characterized by ^1H NMR. Subsequent hydrolysis led to aldehyde **20**.

(13) Nerz-Stomes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489−2498.

Scheme 6



1 to upenamide are construction of the macrocyclic ring system and completion of the spirooxaquinolizidinone ring system.

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

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