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Stereocontrolled Synthesis of the DE Ring System of the Marine Alkaloid Upenamide

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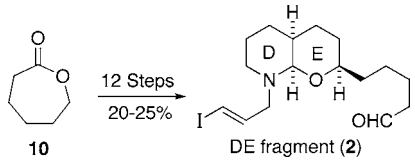
ABSTRACT



A stereocontrolled synthesis of the DE fragment (2) of the marine alkaloid upenamide (1) is described. The synthesis proceeds in 12 steps from caprolactone (10) and 20–25% overall yield.

In 2000, Scheuer and co-workers described the isolation and structure elucidation of upenamide (**1**) from the crude extract of the marine sponge *Echinochalina* sp. collected from Derawan Island, Indonesia (Figure 1).[1] Upenamide (**1**) is a

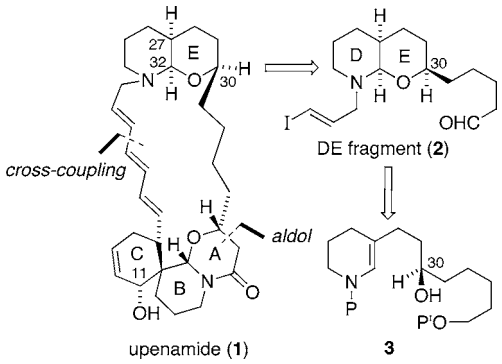


Figure 1. Retrosynthetic analysis of upenamide (**1**).

macrocyclic diamine alkaloid possessing both a unique spirooxaquinolizidinone (ABC) and hemiaminal (DE) ring systems likely biosynthetically derived from a bis-3-alkylpyridine or reduced bis-3-alkylpyridine.[2] The structure of **1** was elucidated by a combination of spectroscopic and accurate mass measurements. The absolute stereochemistry of the spirooxaquinolizidinone ring system was assigned on the basis of ^{1}H NMR analysis of the *S*- and *R*-Mosher esters derived at the C(11) hydroxyl group, while the absolute stereochemistry of the DE ring system was not assigned. Thus, the collective structural information currently available for upenamide is in agreement with both 27*R*,30*S*,32*S* and 27*S*,30*R*,32*R* configurations (only the latter isomer is shown in Figure 1). Unambiguous assignment of upenamide as one of these two stereoisomers will require a total synthesis followed by structural correlation. Herein, we describe an enantioselective synthesis of the DE fragment (**2**) of upenamide.

Our synthetic strategy directed toward **1** envisioned DE fragment **2** to be merged with 1 equiv of the ABC fragment of upenamide through a combination of a metal-mediated cross-coupling and stereoselective aldol reactions as illustrated retrosynthetically in Figure 1.[3] This analysis led to the identification of hemiaminal **2** as a key advanced synthetic intermediate. Our approach toward the assembly

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(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) Reviews on 3-alkylpiperidine alkaloids: (a) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765−794. (b) Andersen, R. J.; Van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, W. W., Ed.; Pergamon: New York, 1996; Vol. 10, Chapter 3.

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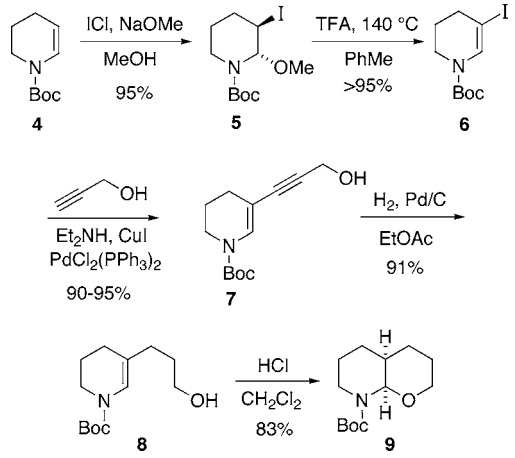
of **2** relies on an acid-catalyzed cyclization of enamine **3**. *The success of this approach critically depends on the stereoselectivity of the cyclization of* ***3*** *that could deliver up to four stereoisomers.* As a preliminary study, we elected to first examine the cyclization of enamine **8** (Scheme 1) to evaluate the inherent cis/trans ring fusion stereoselectivity.

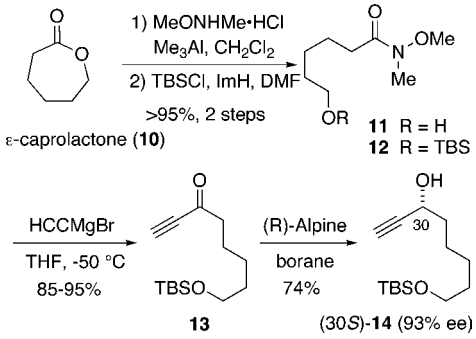
Scheme 1



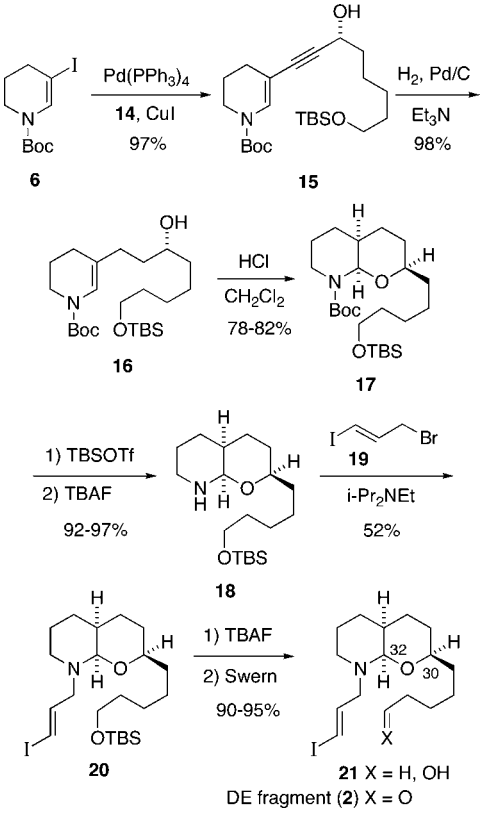
Synthesis of enamine **8** started from β-iodoenecarbamate **6**, produced in two steps from enecarbamate **4** (Scheme 1).[4] To this end, iodomethoxylation of **4** provided adduct **5** as a single stereoisomer which without purification was heated in toluene containing a trace amount of trifluoroacetic acid. Under these conditions, elimination of methanol was complete in 5−10 min to afford iodoenecarbamate **6** in near quantitative yield.[5] Iodoenecarbamate **6** was coupled with propargyl alcohol under Sonogashira coupling conditions to afford **7** in excellent yield.[6] Next, reduction of the carbon−carbon triple bond of **7** was effected without reduction of the enecarbamate carbon−carbon double bond by adding 2 equiv of triethylamine to the hydrogenation reaction mixture. Exposure of enecarbamate **8** to hydrochloric acid in dichloromethane led to a rapid and stereoselective cyclization to give hemiaminal **9** as a single stereoisomer in 75% yield over two steps. The ring fusion stereochemistry was assigned based on the small constant observed between the ring fusion protons (ca. $J < 2$ Hz) and chemical shift of the hemiaminal proton ($\delta > 4.0$) of **9**.[7] We next turned our attention toward the enantioselective preparation of enamine **3** which required the preparation of secondary alcohol (30*S*)-**14**.

The synthesis of propargyl alcohol (30*S*)-**14** is outlined in Scheme 2 starting from ϵ-caprolactone (**10**). Condensation of caprolactone with *N*,*O*-dimethylhydroxylamine hydrochloride followed by alcohol silylation gave amide **12** in near quantitative yield. Reaction of **12** with ethynylmagnesium bromide afforded alkynone **13**. Reduction of **13** using (*R*)-alpine borane gave propargyl alcohol (30*S*)-**14** in 74% yield and 93% ee as determined by chiral GC analysis.[8] Sonogashira coupling of **6** and (30*S*)-**14** provided eneyne **15** in near-quantitative yield (Scheme 3). Reduction of **15** followed by acid-catalyzed cyclization gave **17**, with no other isomers

Scheme 2



Scheme 3



(3) For earlier studies on the synthesis of upenamide, see: (a) Maia, A. A.; Mons, S.; Gil, R. P. D.; Marazano, C. *Eur. J. Org. Chem.* **2004**, 1057−1062. (b) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181−4183.

(4) Prepared by electrochemical oxidation: (a) Shono, T. *Tetrahedron* **1984**, *40*, 811−850. (b) Eberson, L.; Hlavaty, J.; Jonsson, L.; Nyberg, K.; Servin, R.; Sternerup, H.; Wistrand, L. G. *Acta Chem. Scand. B* **1979**, *33*, 113−115. (c) Nyberg, K. *Synthesis* **1976**, 545−546.

(5) (a) Matos, M. N.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron* **2005**, *61*, 1221−1244. (b) Matos, M. N.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron Lett*. **2001**, *42*, 7007−7010.

(6) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (b) Sonogashira, K. In *Comprehensive Oganic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.4.

(7) Duhamel, P.; Deyine, A.; Dujardin, G.; Ple, G.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2103−2114.

observed. Removal of the Boc protecting group required initial conversion to the TBS carbamate followed by fluoride treatment as described by Ohfune and Sakaitani.[9] Purification of **18** by flash chromatography resulted in significant epimerization of the C32 stereocenter to afford a 3.6:1 mixture of **18** and the corresponding trans ring fusion isomer. Epimerization was completely suppressed when 1% triethylamine was included in the flash chromatograpy eluant. Allylation of **18** with allyl bromide **19** afforded **20** in 52% yield. Removal of the TBS protecting group followed by Swern oxidation completed the synthesis of **2**. The relative stereochemistry between C30 and C32 was assigned on the basis of an observed NOE between H_{32} and H_{30} (Figure 2).

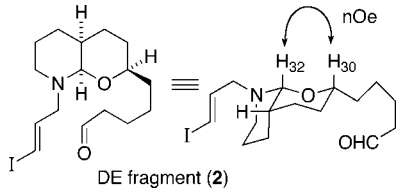
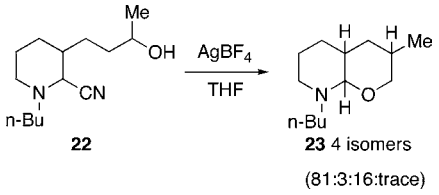


Figure 2. Observed NOE between H_{30} and H_{32}.

The cis ring fusion stereochemistry was assigned on the basis of the observed small coupling constant (ca. $J < 2$ Hz) and chemical shift of the hemiaminal proton ($\delta > 4.0$).[7]

In their studies on developing an approach to the DE ring system of upenamide, Marazano and co-workers observed that treatment of **22** with silver tetrafluoroborate in tetrahydrofuran resulted in the production of four isomers (**23**) in a ratio of 81:3:16:trace.[3a] The major isomer had the same relative configuration as the corresponding ring system of upenamide. This result contrasts our observation where treatment of **16** resulted in the production of a *single* stereoisomer (**17**). We believe our results reflect a kinetic reaction while the reaction products of the silver(I) assisted cyclization of **22** (Scheme 4) are produced under thermodynamic conditions. The major difference between enamine **16** and piperidine **22** is the nature of the substituent on the ring nitrogen. In the case of **16** a carbamate group favors a kinetic reaction while an alkyl group on **22** favors a thermodynamic reaction (i.e., the cyclization of **22** is reversible). A rational for the acid-catalyzed cyclization of **16** to afford **17** is given in Figure 3 starting with protonation of enecarbamate **16** to produce an equilibrium mixture of immonium ion isomers **24a** and **24b**. Kinetically, cyclization of **24b** to oxonium ion **26b** is favored relative to the

Scheme 4



cyclization of **24a** to **26a** ($K_a < K_b$), the former positioning the C30 alkyl group in a less hindered pseudoequatorial position in transition state **25b**.

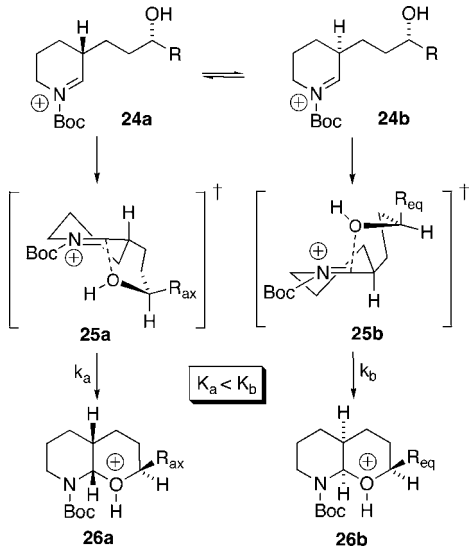


Figure 3. Mechanistic rational for the selective formation of **17** via **26b**.

In summary, we have completed a stereocontrolled synthesis of the DE fragment of upenamide (**2**). Progress on the total synthesis and assignment of structure of upenamide will be reported in due course.

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Supporting Information Available: Full characterization data and experimental procedures for **2**, **5**−**9**, and **11**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051993E

(8) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371−1380.

(9) (a) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543−5546. (b) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876.