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The First Synthesis of the ABC-Ring System of ‘Upenamide

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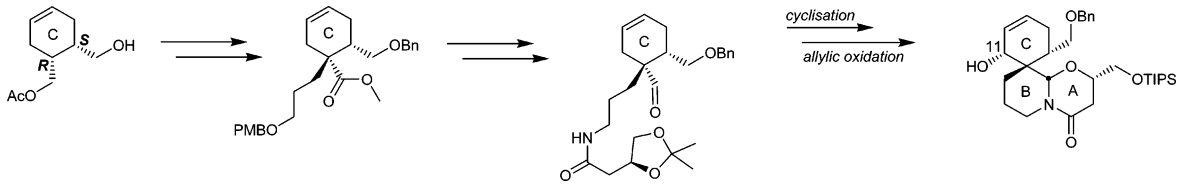
ABSTRACT



The first synthetic route to the spirooxaquinolizidinone core (ABC core) of the macrocyclic marine alkaloid ‘upenamide (1) has been developed. All five stereocenters were introduced with complete stereocontrol. The hydroxyl group at C-11 was introduced by a regio- and stereoselective SeO_2-mediated allylic oxidation. The spirocyclic skeleton was formed by a stannous chloride induced deacetalization–bicyclization procedure. Further stereocenters were introduced by an enzymatic desymmetrization and by incorporation of an (*S*)-malic acid derived building block.

The macrocyclic marine alkaloid ‘upenamide (**1**) was isolated from the branching sponge *Echinochalina* sp. found in the coastal waters of Derawan Island, Indonesia (Figure 1).[1]

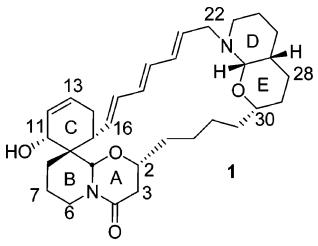


Figure 1. Structure of ‘upenamide (**1**).

The name is coined from ‘*upena*, a Hawaiian word meaning fishing net or trap. ‘Upenamide may be considered as two distinct core units. The ABC core comprises a novel tricyclic spirooxaquinolizidinone system and accounts for five of the eight stereocenters in ‘upenamide. The DE ring system comprises an unusual octahydropyrano[2,3-*b*]pyridine system and contains the remaining three stereocenters. The C and D rings are linked by an all-*trans* triene system. A fully saturated aliphatic chain then completes the 20-membered macrocycle joining rings A and E.

To the best of our knowledge, no total synthesis of ‘upenamide has been achieved so far. However, in a previous communication, we described a route for the preparation of a model ABC spirocyclic core of ‘upenamide,[2] which was adopted by Ong and co-workers for the construction of an organoiron complex of an ABC model core.[3] This methodology was utilized for the preparation of novel polycyclic heterocycles and was published recently.[4] Subsequently, we reported stereoselective syntheses of the DE bicyclic system.[5] In addition, Marazano et al. published the synthesis of a model of the DE core in racemic form,[6] and more recently, Sulikowski et al. reported the stereo- and enantiocontrolled synthesis of an advanced intermediate containing

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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.
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(3) Han, J. L.; Ong, C. W. *Tetrahedron* **2007**, *63*, 609.
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the DE bicyclic system.[7] In this article, we report investigations leading to the first synthesis of the ABC spirocyclic ring system of 'upenamide in enantiopure form.

In preliminary studies, we developed a tin(II) chloride-induced deacetalization−bicyclization process to prepare novel ABC analogues of 'upenamide.[2] We planned to prepare cyclization precursor **3a** and investigate the deacetalization−bicyclization to furnish the fully functionalized spirooxaquinolizidinone **2a** (Figure 2). Unfortunately, all attempts

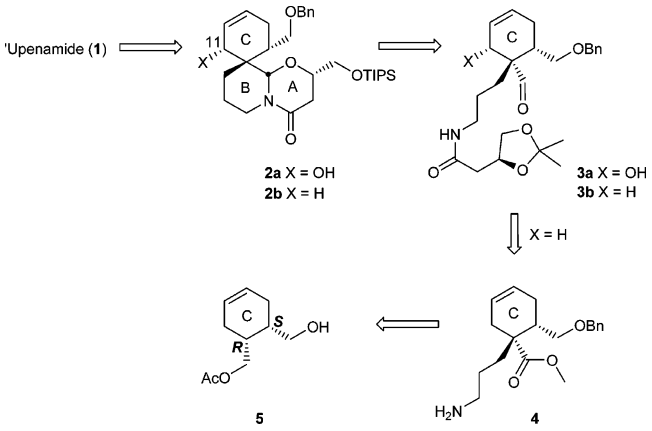
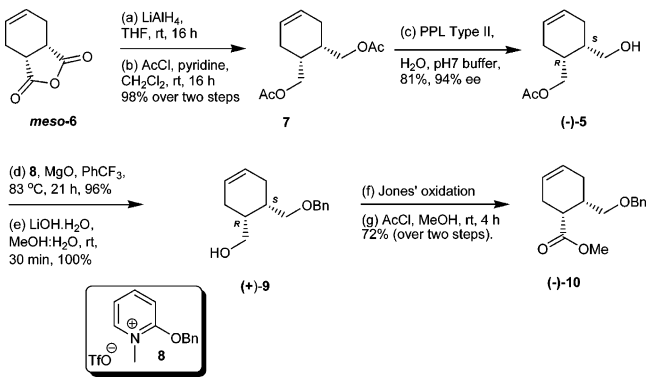


Figure 2. Retrosynthetic analysis of **2a**, the ABC core system of 'upenamide.

to prepare **3a** were unsuccessful. Attention was therefore turned to the preparation of analogue **2b** with the aim of investigating allylic hydroxylation at a late stage of the synthesis. We therefore required compound **3b** and anticipated that methyl ester **4** would be a suitable precursor. This retrosynthetic analysis suggested the use of substituted cyclohexene derivative **5** as starting material, a compound readily available in enantiomerically pure form from inexpensive *meso*-anhydride **6**.[8]

Alcohol (−)-**5** was therefore prepared following a desymmetrization procedure published by von Langen et al. (Scheme 1).[8] It is noteworthy that in our hands this procedure

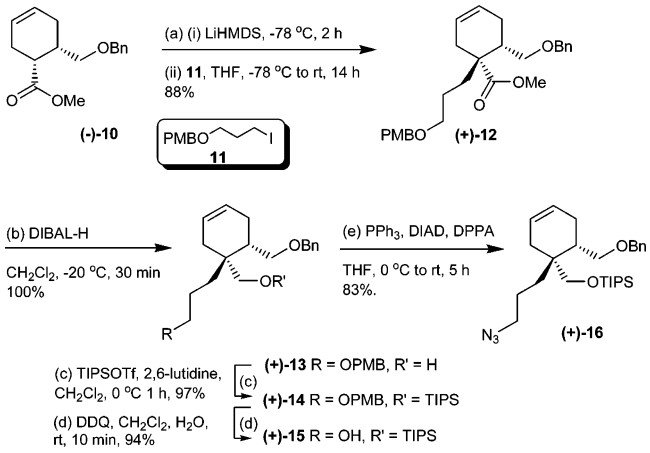
Scheme 1



was scalable to a 0.1 mol scale. *Meso*-anhydride **6** was reduced and bisacetylated to furnish compound **7** via the intermediate diol. Bisacetate **7** was subsequently desymmetrized using *porcine pancreatic lipase* (Sigma type II) to give alcohol (−)-**5** in good yield and 94% enantiomeric excess as determined by ^{1}H NMR analysis of the respective (+)- and (−)-Mosher ester derivatives.[9] The free primary alcohol was subsequently benzyl protected under neutral conditions using Dudley's reagent **8**[10] to give an orthogonally protected cyclohexene diol in excellent yield. It is noteworthy that no transesterification was observed under these conditions. The acetate was saponified, and the resulting free primary alcohol (+)-**9** was oxidized to the carboxylic acid, which was taken on without further purification and converted into methyl ester (−)-**10** by stirring in methanolic HCl.

The quaternary center adjacent to the ester moiety was installed by formation of the lithium enolate followed by trapping with the known iodide **11**.[11] Cyclohexene (+)-**12** was isolated in good yield with only the desired diastereomer, resulting from alkylation from the less-hindered face of the lithium enolate, being obtained (Scheme 2). It was found

Scheme 2



that use of the lithium enolate together with the soft alkyl iodide **11** prevented competing O-alkylation. The methyl ester was then reduced using DIBAL-H to give primary alcohol (+)-**13**. The alcohol was protected as the triisopropylsilyl ether following the Corey procedure.[12] Subsequent PMB deprotection using 2,3-dichloro-5,6-dicyano *para*-benzoquinone (DDQ)[13] and introduction of the azide moiety

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(7) Kiewel, K.; Luo, Z.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 5163.
(8) von Langen, D. J.; Tolman, R. L. *Tetrahedron: Asymmetry* **1997**, *8*, 677.
(9) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.
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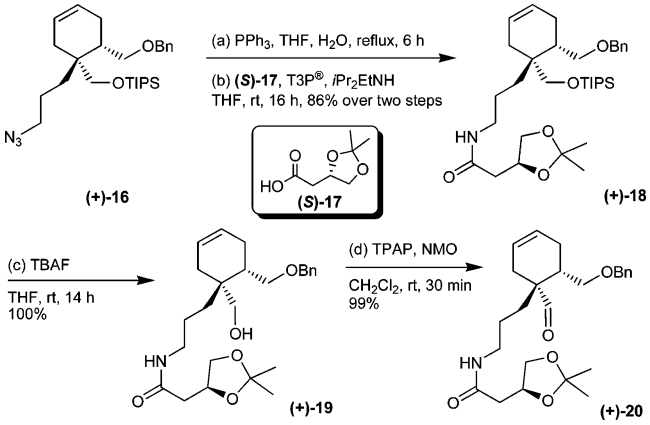
under Mitsunobu conditions[14] produced compound (+)-**16** efficiently in 73% yield over four steps.

The reduction of the azide to the amine was accomplished under Staudinger conditions (Scheme 3).[15] The amine could

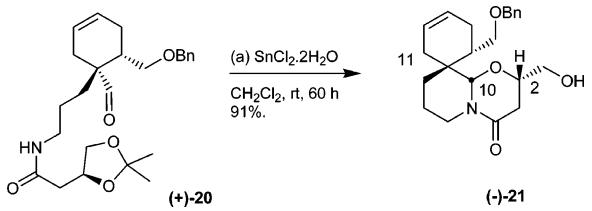
Scheme 3



not be purified by conventional methods and was used directly in the subsequent step in which the (*S*)-malic acid derived acid (*S*)-**17**[16] was coupled to the unpurified amine using propane phosphonic acid anhydride[17] (T3P) to give amide (+)-**18** in good yield. The triisopropylsilyl ether was cleaved using tetra-*n*-butylammonium fluoride (TBAF), and the resulting primary alcohol (+)-**19** was oxidized to the aldehyde using Ley's catalytic tetra-*n*-propylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) procedure[18] to furnish aldehyde (+)-**20** in near quantitative yield.

At this stage, we were in a position to attempt the crucial cyclization by subjecting aldehyde (+)-**20** to tin(II) chloride dihydrate conditions to induce deacetalization−bicyclization. Gratifyingly, the 11-deoxy ABC core (−)-**21** of 'upenamide was formed in 91% yield and excellent diastereoselectivity, affording only the product with the hemiaminal proton (H-10) being *syn* to H-2 (Scheme 4). This

Scheme 4



was expected and can be rationalized by the thermodynamically more stable product forming under these equilibrating conditions.[2] Compound (−)-**21** showed no Bohlmann bands in its IR spectrum suggesting the absence of a *trans*-oxaquinolizidine system.[19] In addition to that, the stereochemistry was confirmed by ^{1}H NMR studies (NOE between H-2 and H-10 as well as δ_C (C-10) 93.3 ppm) and was later validated by the synthesis of the crystalline 9-anthracenoyl derivative (−)-**22** (Figure 3).[20]

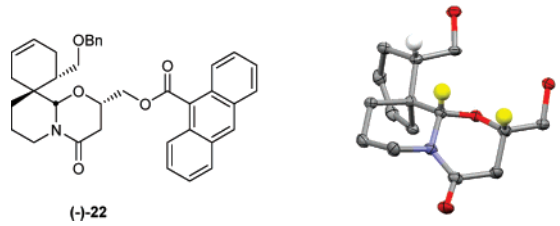
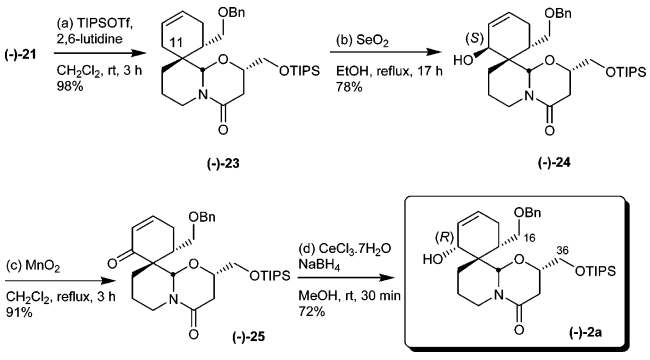


Figure 3. Spirooxaquinolizidinone (−)-**22**, the 9-anthracenoyl ester derivative of (−)-**21**. Note that the benzyl ether and anthracenoyl ester are not shown for clarity (X-ray depicted using Mercury 1.4).

We were now faced with the challenge of introducing the required hydroxyl group at C-11 (numbering in accordance with Figure 1). In the late 1930s, Guillemonat postulated a set of rules for the selectivity of allylic oxidations using selenium(IV) oxide. He found that hydroxylation of an allylic position in a ring normally occurs regioselectively adjacent to the more substituted end of the double bond.[21] We therefore expected a regio- and stereoselective hydroxylation in favor of the (*S*)-epimer at C-11. Indeed it was found that after triisopropylsilyl ether protection of the free hydroxyl giving compound (−)-**23** selenium(IV) oxide hydroxylation occurred selectively at C-11 giving selectively the (*S*)-epimer (−)-**24** (Scheme 5). Inversion of this center was accomp-

Scheme 5



lished by a manganese(IV) oxide-mediated oxidation of the secondary alcohol to the corresponding enone (−)-**25** and

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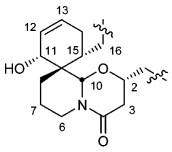
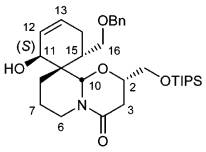
by reducing the enone under Luche conditions[22] to give the desired (*R*)-epimer (−)-**2a**. The respective epimers were assigned by comparing their NMR data with those published in the isolation paper of 'upenamide.[1] The NOE correlation and ^{13}C NMR chemical shifts of C-11 were particularly characteristic (Table 1).

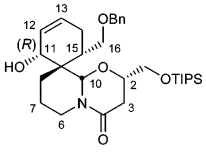
Table 1. NMR Data Comparison of 'Upenamide (**1**) and the ABC Cores (−)-**24** and (−)-**2a**[a]



'upenamide (**1**)



(-)-**24**



(-)-**2a**

compound	^{13}C (C-11)	NOE (H-11)
1	70.0	12, 15
(−)-**24**	64.9	2, 3, 7, 10, 16
(−)-**2a**	70.1	12, 15

[a] The spectrum of 'upenamide (**1**) was recorded in CD_3OD at 500 MHz for ^1H NMR and at 125 MHz for ^{13}C NMR, and the spectra for the ABC cores (−)-**24** and (−)-**2a** were recorded in CD_3OD at 400 MHz for ^1H NMR and at 100 MHz for ^{13}C NMR spectroscopy.

In summary, the first synthetic route to the spirooxaquinolizidinone core (ABC core) of the macrocyclic marine alkaloid 'upenamide (**1**) has been developed. The four stereocenters of the 11-deoxy fragment (−)-**21** were introduced by an enzymatic desymmetrization of *meso*-diacetate **7**, followed by a diastereoselective alkylation of ester (+)-**10** to give ester (+)-**12**. This was followed by an amide coupling with the (*S*)-malic acid derived acid (*S*)-**17** and a subsequent *syn*-selective deacetalization−bicyclization procedure to furnish the 11-deoxy ABC core (−)-**21**. The hydroxyl group at C-11 was introduced by a regioselective allylic hydroxylation giving the (*S*)-epimer (−)-**24** in a stereoselective manner. The stereocenter was inverted by a MnO_2-mediated oxidation followed by a stereoselective Luche reduction to give the fully functionalized ABC core fragment (−)-**2a**. It should be noted that the tricycle (−)-**2a** is ideally functionalized for further elaboration at C-16 and C-36 (numbering in accordance with the isolation paper). With both core systems synthesized by our group, efforts are now underway to complete the total synthesis of 'upenamide (**1**).

Acknowledgment. We are grateful to Dr. A. C. Whitwood (University of York) for carrying out the crystallography study. The financial support by AstraZeneca (J.P.S.), the University of York (G.D.M., J.P.S., S.B.R.), as well as the EPSRC (M.R.) is gratefully acknowledged as is the assistance of Dr. A. Wells (AstraZeneca, Charnwood) with scaling up the enzymatic desymmetrization process. We thank Archimica for their kind donation of T3P.

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

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