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A concise Diels–Alder strategy leading to congeners of the ABC ring system of the marine alkaloid 'upenamide

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ABSTRACT

A second-generation approach to the BC spirocycle of 'upenamide is reported. Central to the synthesis is an endo selective Diels–Alder reaction between 1-(*t*-butyldimethylsiloxy)-1,3-butadiene and bromomaleic anhydride followed by a radical mediated allylation of the ring fusion bromide. Functional group manipulation provides three (**9**–**11**) advanced synthetic intermediates ready for coupling with the remaining half (DE bicycle) of 'upenamide.

In 2000 Scheuer and co-workers described the isolation and structure elucidation of 'upenamide, a unique macrocyclic alkaloid from the Indonesian sponge *Echinochalina* sp.[1] The structure of 'upenamide features a tricyclic and a bicyclic hemiaminal ring system connected by an unsaturated macrocyclic core (Fig. 1). While a biosynthetic pathway leading to 'upenamide can be conceived based on comparison to structurally similar 3-alkylpiperidine marine natural products such as the manzamines and haliclonacyclamines, complete structural assignment of 'upenamide awaits clarification by total synthesis.[2,3]

Our group[4] and the Taylor[3,5] group have developed synthetic routes to key intermediates leading to an ABC tricyclic ring system progenitor and DE bicyclic ring system.[6] In assembling the former structure, both our group and Taylor's group took advantage of stereocontrolled Diels–Alder reactions leading to appropriately substituted cyclohexene (C ring) intermediates (Scheme 1). As summarized in Scheme 1 our group used the cycloadduct derived from 1-(*t*-butyldimethylsiloxy)-1,3-butadiene and 2-bromo-5-(methoxy)furan-2(5*H*)-one to access aldehyde **II** by way of a six-step reaction sequence and vinyl iodide **III** by way of the Takai olefination of **II** (Scheme 1).[4b] The Taylor group produced aldehyde **V**, differing only in silyl protecting group relative to **II**, starting from cyclohexene **IV**.[5c,d] Overall, a 12-step reaction sequence was required to advance **IV** to imine **VI**.

Common strengths of ours and Taylor's synthetic routes are the use of endo selective Diels–Alder reactions followed by stereoselective alkylation reactions to install the three contiguous stereocenters contained within the C ring of 'upenamide including the central quaternary carbon. We identified two significant problems in our approach to BC spirocycle (**II** and **III**), namely the propensity of the C15 aldehyde to undergo epimerization (partly due to electrostatic interaction with the C10 amide carbonyl) and, second, the required adjustment of oxidation state of the C10 carbon. We desired access to the equivalent of a differentiated bis-aldehyde intermediate (cf. Fig. 1, ABC tricycle precursor). With these objectives in mind, we describe herein a simplified and expedient approach to ABC tricycle precursors starting with a Diels–Alder reaction between 1-(*t*-butyldimethylsiloxy)-1,3-butadiene and bromomaleic anhydride (Scheme 2).

To our surprise bromomaleic anhydride (**2**) has found limited utility in natural product synthesis (Scheme 2).[7] We found the Diels–Alder reaction between **1** and **2** to be quite facile to affording crystalline adduct **3** in 76–80% yield as a single (endo) isomer. Radical mediated allylation of **3** with allyltributylstannane (AIBN, toluene, 90 °C, μW, 45 min)[8] provided desired **4a** and **4b** in 65% and 23% yields, respectively.[9] Reduction of anhydride **4a** to diol **5** was examined using a variety of reducing reagents. Reduction of anhydride **4** with lithium aluminum hydride produced triol **6** in 65–70% yield accompanied by diol **5** (9% yield).[10] Optimal conditions for production of TBS ether **5** employed L-Selectride as the reductant in THF at 0 °C to provide **5** in 43% yield without observation of triol **6**.

Orthogonal protection of diol **5** allowed controlled functionalization that was accomplished by tritylation of the less hindered alcohol (Ph_3Cl, Et_3N, DMAP, DMF, 97%) followed by acetylation (Ac_2O, pyridine, 86%) of the remaining primary alcohol to afford

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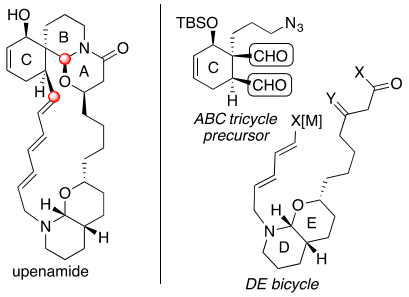
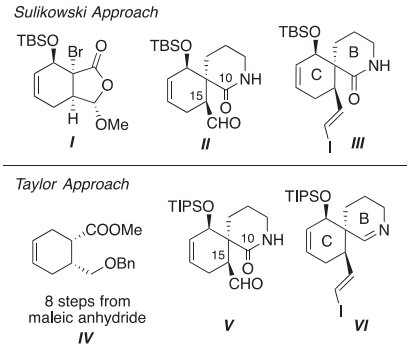
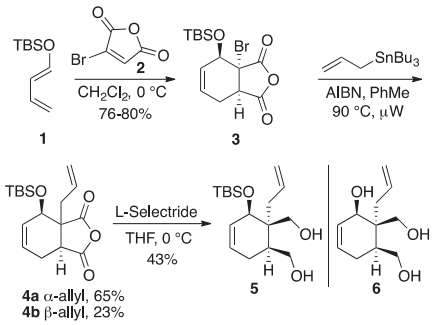


Figure 1. Structure of 'upenamide and advanced synthetic intermediates.

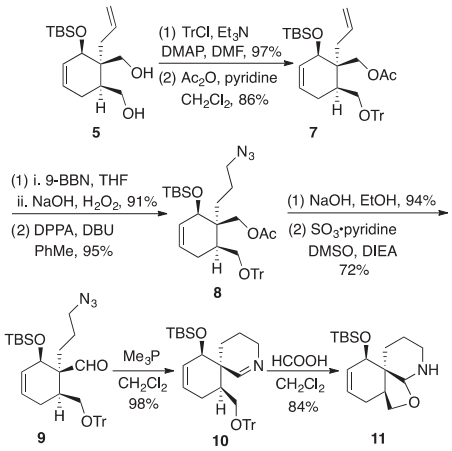


Scheme 1. Synthetic routes to upenamide BC spirocycle.



Scheme 2. Synthesis of diol **5**.

orthogonally protected triol **7**. Hydroboration–oxidation of the terminal alkene afforded a hydroxyl group available for conversion to azide **8**. The desired functional group interconversion was readily achieved using diphenylphosphoryl azide and DBU. Removal of the acetate group released the internal alcohol which following oxidation under Parikh–Doering conditions gave aldehyde **9** in 72% yield. The key Staudinger cyclization was affected using trimethylphosphine to give imine **10** in 98% yield. Removal of the trityl protecting group released the remaining primary alcohol resulting in subsequent cyclization to give aminal **11**. Notably, advanced intermediates **9**, **10,** and **11** (Scheme 3) are of utility in advancing a total synthesis of 'upenamide (cf. Fig. 1).



Scheme 3. Synthesis of BC spirocycle and ABC tricycle precursors **9**–**11**.

In conclusion, we described a concise route leading to advanced synthetic intermediates ready to serve as progenitors to the ABC tricycle within the context of an'upenamide total synthesis. When compared to our earlier synthetic efforts the described 9 to 11 step reaction sequence leading to intermediates **9**–**11** compare favorably.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.102.

References and notes

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. 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.
3. Unsworth, W. P.; Taylor, R. J. K. *Org. Biomol. Chem.* **2013**, *11*, 7250–7261.
4. (a) Kiewel, K.; Luo, Z.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 5163–5165; (b) Luo, Z.; Peplowski, K.; Sulikowski, G. A. *Org. Lett.* **2007**, *9*, 5051–5054.
5. (a) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181–4183; (b) Menard-Moyon, C.; Taylor, R. J. K. *Eur. J. Org.* **2007**, 3698–3706; (c) Schmidt, J. P.; Beltran-Rodil, S.; Cox, R. J.; McAllister, G. D.; Reid, M.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 4041–4044; (d) Unsworth, W. P.; Gallagher, K. A.; Jean, M.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 262–265.
6. Other synthetic approaches to upenamide: (a) Maia, A. A.; Mons, S.; Gil, R. P. D.; Marazana, C. *Eur. J. Org. Chem.* **2004**, 1057–1062; (b) Han, J. L.; Ong, C. W. *Tetrahedron* **2007**, 609–614.
7. Apponyi, M. A.; Bowie, J. H.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **2002**, *55*, 343–348.
8. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829–5831.
9. Stereochemistry assigned based on nOe analysis of **4a** and **4b**.
10. For examples of loss of silyl protecting groups during LAH reduction, see: (a) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105–2108; (b) de Vries, E. F. J.; Brussee, J.; van der Gen, A. *J. Org. Chem.* **1994**, *59*, 7133–7137.