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Synthesis of the Fused Polyether Core of Hemibrevetoxin B by Two-Directional Ring-Closing Metathesis

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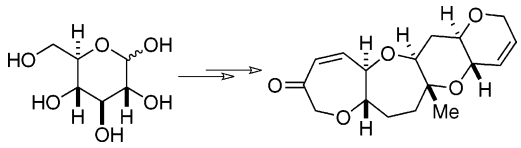
ABSTRACT



The tetracyclic fused polyether core of the marine natural product hemibrevetoxin B has been prepared in an efficient manner by using a strategy in which ring-closing metathesis (RCM) reactions were employed for ring synthesis. Simultaneous construction of the A and D rings was accomplished by double two-directional RCM of a tetraene.

Hemibrevetoxin B was first isolated from cultured cells of the marine dinoflagellate *Karenia brevis* (previously known as *Gymnodinium breve*) by Shimizu and Prasad in 1989 and is the smallest member of the fused polycyclic ether family of marine natural products (Scheme 1).[1] Even though it is significantly smaller than the other brevetoxins and structurally related compounds, such as the ciguatoxins and yessotoxins, hemibrevetoxin B is a formidable synthetic target possessing four *trans*-fused cyclic ethers (A−D) and 10 stereogenic centers. It also presents many of the synthetic challenges found in larger congeners such as brevetoxin B (e.g., rings D−G and I−K). Although hemibrevetoxin B has been a very popular synthetic target, only four rather lengthy total syntheses and four formal syntheses have been published to date.[2,3] A short and highly efficient total synthesis of hemibrevetoxin B has yet to be completed.

Our retrosynthetic analysis of hemibrevetoxin B is shown in Scheme 1. Removal of the enal-containing side chain from the A-ring reveals the late-stage intermediate **i**. Cleavage of the D-ring methyl substituent gives ketone **ii** and disconnection of the D-ring hexadiene side chain and the oxygen-containing substituents from the A-ring leads to the tetracyclic intermediate **iii**. A double ring-closing metathesis (RCM) disconnection then reveals the bicyclic tetraene **iv**. Removal of the allyl group, the enone substituent, and the terminal methylene of the vinyl group produces the bicyclic triol **v**. Subsequent opening of the B-ring and acetal formation leads to the C-ring diol **vi**. Further disconnection of the methyl group and the hydroxypropyl side chain delivers the simplified C-ring unit **vii** and a further RCM

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(1) Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476−6477.

(2) For total syntheses, see: (a) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935−7936. (b) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558−3575. (c) Kadota, I.; Jungyoul, P.; Koumura, N.; Pollaud, G.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5777−5780. (d) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365−6368. (e) Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6597−6606. (f) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822−7824.

(3) For formal syntheses, see: (a) Yamamoto, Y.; Kadota, I. *Bull. Soc. Chim. Belg.* **1994**, *103*, 619−628. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200−6209. (c) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380−1386. (d) Fujiwara, K.; Sato, D.; Watanabe, M.; Morishita, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 5243−5246.

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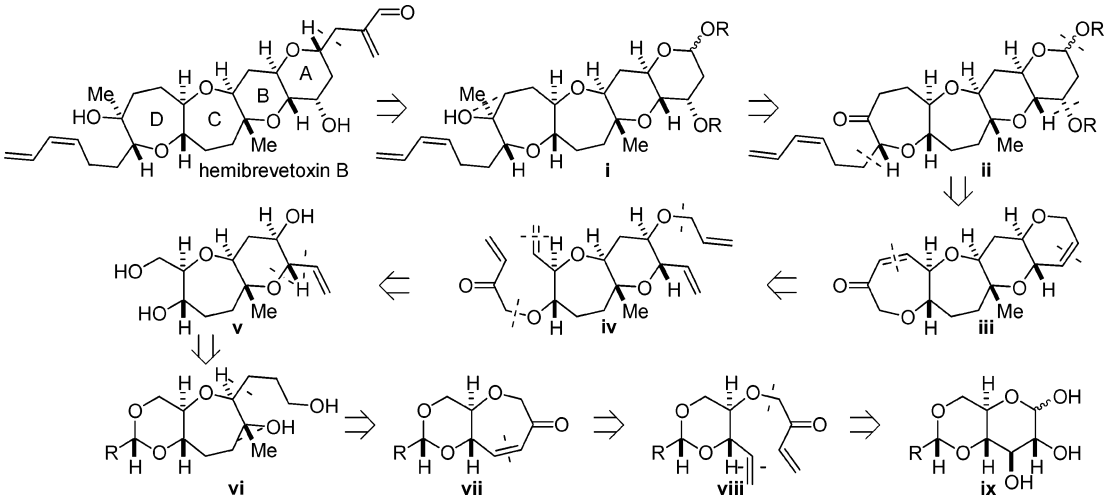
Scheme 1



disconnection gives the enone **viii**, which then suggests the glucose acetal **ix** as a chiral pool starting material.

The central feature of our synthetic strategy was to be the deployment of a double two-directional RCM reaction for simultaneous construction of the A and D rings of hemibrevetoxin B from a precursor bearing an enone and an allyl ether (**iv** → **iii**). In principle, a two-directional strategy could be adopted for construction of the B and C rings, but for the purposes of this study we chose to assemble this bicyclic system sequentially. We have previously reported that double two-directional RCM is a powerful method for the preparation of a variety of fused tricyclic systems possessing various combinations of rings,[4] and have recently applied iterative two-directional RCM to the synthesis of pentacyclic F−J fragments of the gambieric acids.[4b] However, prior to embarking on this study we had not explored the feasibility of using enones as reaction partners in two-directional RCM reactions.

The starting material for our synthesis was the commercially available glucose derivative **1** (Scheme 2). Periodate cleavage and immediate Wittig methylenation of the resulting aldehyde afforded the alcohol **2**, which was converted into the RCM precursor **4** by etherification with 3-chloro-2-oxopropylidene triphenylphosphorane (**3**) and reaction of the resulting stabilized phosphonium ylide with formaldehyde under buffered conditions.[5,6] Ring-closing metathesis of the enone **4** using the ruthenium complex **5** (3 mol %) in dichloromethane at reflux provided the crystalline oxepenone **6** in 94% yield.[6] The structure of this compound and stereochemical assignments were confirmed by X-ray crystallography.[7]

Introduction of a side chain by direct deprotonation of the α,β-unsaturated ketone **6** and alkylation of the resulting enolate was extremely problematic and poor yields of the required product were obtained. To circumvent these problems, the ketone **6** was converted into the corresponding *N*,*N*-dimethylhydrazone **7** (Scheme 2).[8] Sequential deprotonation of the hydrazone **7** with *tert*-butyllithium, alkylation with 3-benzyloxy-1-iodopropane, and subsequent hydrazone hydrolysis afforded the diastereomeric alkylated ketones **8** and **9** as a 1:1 mixture in reasonable yield. After partial separation of the isomeric alkylation products, material enriched in unrequired ketone **8** (1:2.5, **9:8**) was epimerized by treatment of the mixture with DBU in benzene at rt to give predominantly the required ketone **9** (4.5:1, **9**:**8**). Treatment of the ketone **9** with methylmagnesium bromide at low temperature gave a tertiary allylic alcohol in excellent yield as a single isomer. Alkene reduction and hydrogenolysis of the benzyl ether were then accomplished simultaneously by treatment of the tertiary allylic alcohol with hydrogen in the presence of Pearlman's catalyst. The required diol **10** was isolated as a crystalline solid in 99% yield and its structure was confirmed by X-ray crystallography.[7]

Installation of the B-ring was accomplished by using the route shown in Scheme 3. Dehydration of the side chain in the diol **10** to give the alkene **11** was achieved in a one-pot fashion by conversion of the primary hydroxyl group into the corresponding 2-nitrophenylselenide, treatment of this selenide with hydrogen peroxide, and subsequent in situ thermal elimination.[9] Conversion of the hindered tertiary alcohol **11** into the alkynyl ether **12** was achieved by using Greene's procedure[10] in the manner previously described by

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(7) Crystallographic data (excluding structure factors) for the compounds **6**, **10**, **14**, and **23** have been deposited (**6** CCDC 626520; **10** CCDC 626521; **14** CCDC 626522; **23** CCDC 626523) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax +44-(0) 1223 336033, e-mail deposit@ccdc.cam.ac.uk]. CIF files are available as Supporting Information.

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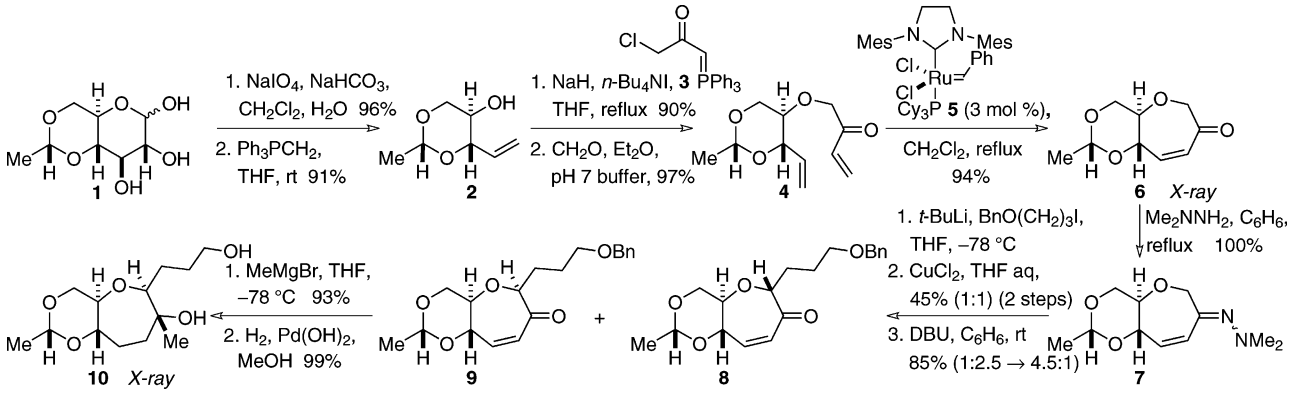
Scheme 2



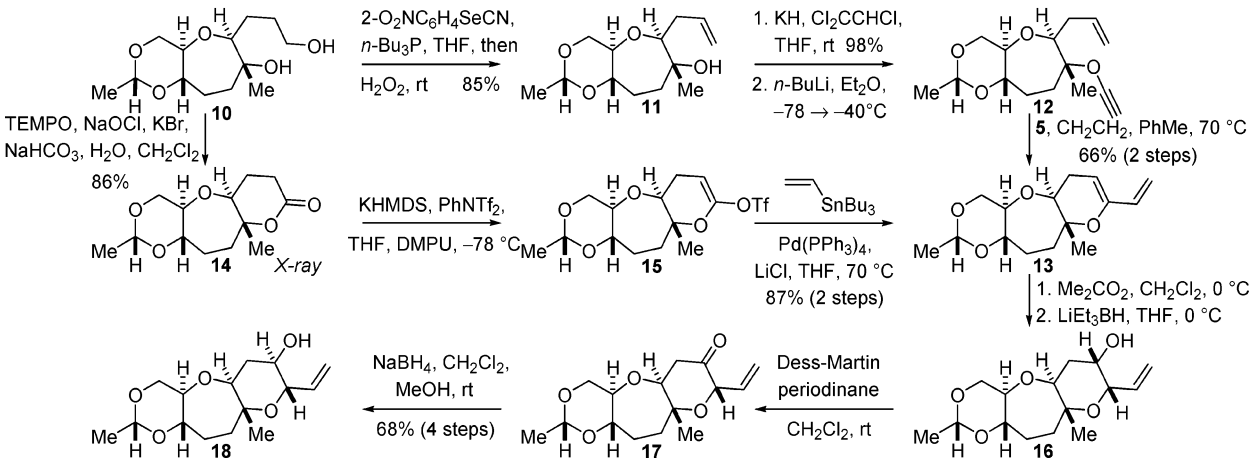
us for the synthesis of related systems.[4,11] Ring-closing enyne metathesis mediated by the ruthenium complex **5** then afforded the tricyclic diene **13**. Unfortunately, alkynyl ether formation and the RCM reaction were complicated by the propensity of the alkynyl ether to undergo a thermal retro-ene reaction resulting in fragmentation to give an allylic ether and ketene.[12] Alkynyl ethers possessing highly branched alkoxy groups (such as ours) show enhanced susceptibility to the retro-ene reaction,[12b] and in our case, highly variable yields were obtained depending on the reaction scale and workup procedure employed.

To circumvent the retro-ene problem, an alternative sequence was investigated. The diol **10** was first converted into the crystalline lactone **14** by using the oxidative procedure first described by Anelli and co-workers and susbequently applied to a related system by Yamamoto and co-workers.[13] The structure of the lactone **14** was confirmed by X-ray crystallography.[7] Deprotonation of the lactone **14** and immediate enolate trapping with *N*-phenyltrifluoromethanesulfonimide provided the ketene acetal **15**. Subsequent Stille coupling of the triflate **15** with tributylvinyltin, using tetrakis(triphenylphosphine)palladium(0), afforded the diene **13**, which had been obtained from the enyne metathesis reaction already, in excellent yield.[14]

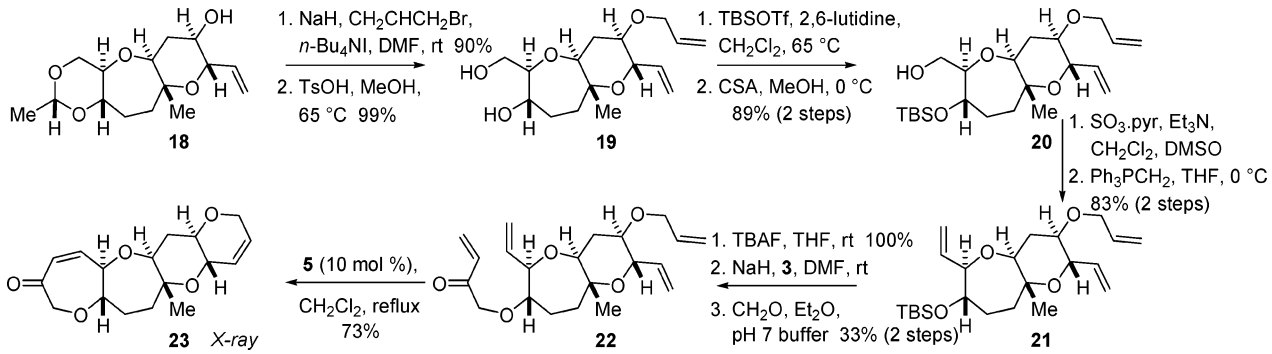
Selective epoxidation of the diene at the electron-rich enol ether site was accomplished by using a freshly prepared solution of dimethyldioxirane at 0 °C. Subsequent regioselective reduction of the resulting vinyl epoxide at the anomeric position was performed by using lithium triethylborohydride to afford the alcohol **16**.[15] At this stage, it was necessary to invert the configuration at the hydroxyl-bearing stereogenic center to give the alcohol **18**; this operation was accomplished by sequential Dess−Martin oxidation[16] and diastereoselective ketone reduction with sodium borohydride.

The synthesis of the complete tetracyclic framework of hemibrevetoxin B was completed as shown in Scheme 4. The alcohol **18** was converted into the corresponding allyl ether by using standard etherification conditions. Removal of the acetal provided the diol **19** in high yield and subsequent formation of the bis-TBS ether followed by selective deprotection of the primary hydroxyl site gave the alcohol **20**. Parikh−Doering oxidation[17] followed by Wittig methylenation of the resulting aldehyde gave the triene **21**. Removal of the TBS group, alkylation with the chloride **3**,

Scheme 3



Scheme 4



and reaction of the resulting stabilized phosphonium ylide with formaldehyde gave the double ring-closing metathesis precursor **22** in modest yield.

It was now possible to effect the key two-directional double RCM reaction. Exposure of the tetraene **22** to the Grubbs second generation ruthenium catalyst (**5**) resulted in simultaneous RCM of both the enone and allylic ether with their proximal vinyl groups and afforded the fused polyether **23** in good yield. The tetracyclic compound was obtained as a crystalline solid and its structure and stereochemical assignments were confirmed by X-ray crystallography.[7]

Elaboration of the fused tetracyclic compound **23** to give hemibrevetoxin B by sequential D-ring alkylation via the hydrazone, introduction of the D-ring methyl substituent, and subsequent A-ring elaboration should be possible. Functionalization of rings A and D to complete the total synthesis of the natural product is in progress and the results of this work will be reported in due course.

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Supporting Information Available: Spectroscopic and other data for the key compounds **6**, **10**, **11**, **13**, **14**, **18**, **22**, and **23** plus X-ray data (CIF files) for compounds **6**, **10**, **14**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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