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A convergent approach to the formal total synthesis of hemibrevetoxin B

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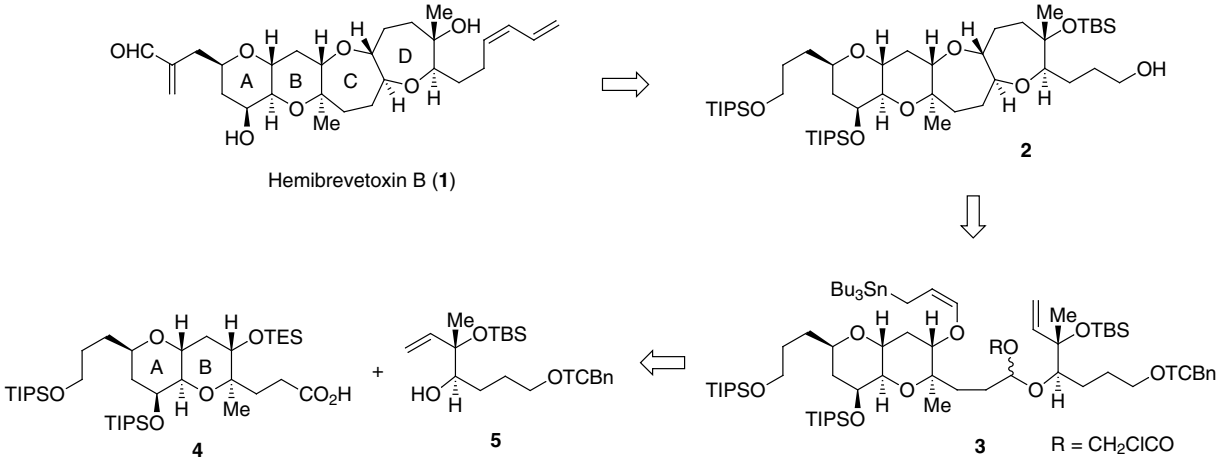
Abstract—A convergent synthesis of the key synthetic intermediate of hemibrevetoxin B was achieved via the intramolecular allylation of an α-chloroacetoxy ether and subsequent ring-closing metathesis.

Hemibrevetoxin B (**1**), which has a 6,6,7,7-tetracyclic ether skeleton including 10 stereocenters, was isolated from the cultured cells of the red tide organism *Gymnodinium breve* by Shimizu and Prasad in 1989.[1] The unique structural features have attracted the attention of synthetic chemists, and a number of strategies have been investigated. To date, seven total syntheses, including three formal syntheses, have been reported.[2] In this letter, we report a convergent formal total synthesis of **1**.

Scheme 1 describes our retrosynthetic analysis of **1**. We focused on the convergent construction of the key intermediate **2**, which was converted to **1** in our previous synthesis,[2c,e] via the intramolecular allylation of α-acetoxy ether **3** followed by ring-closing metathesis.[3] The



Scheme 1. Retrosynthetic analysis of hemibrevetoxin B (**1**).

Keywords: Hemibrevetoxin B; Polycyclic ethers; Convergent synthesis.
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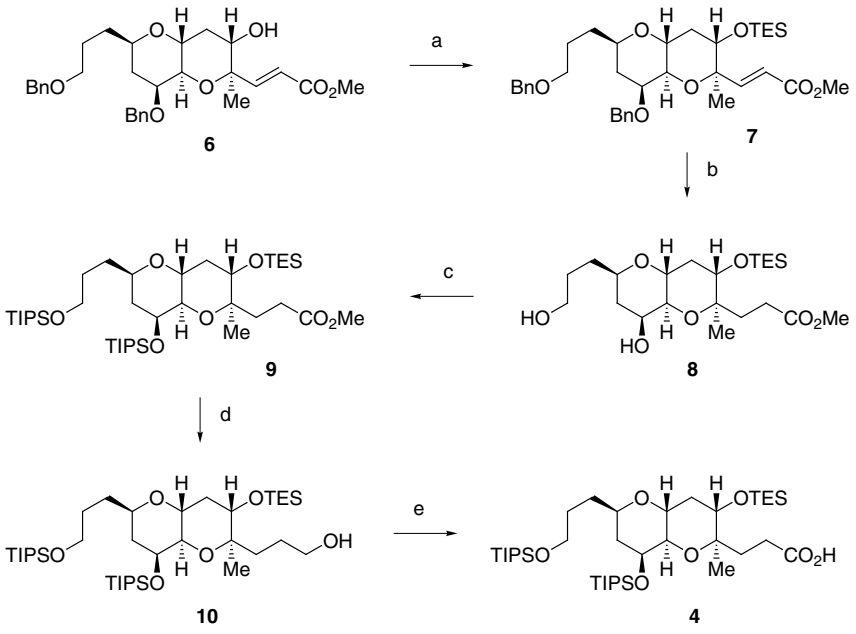
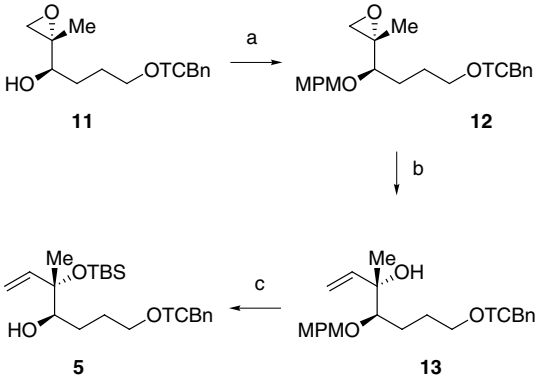


Scheme 2. Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, quant; (b) H_2, $Pd(OH)_2$–C, EtOAc, rt; (c) TIPSOTf, 2,6-lutidine, DMF, rt–70 °C, 71% (two steps); (d) $LiAlH_4$, ether, 0 °C and (e) (i) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C; (ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, THF–H_2O, 0 °C.

cyclization precursor **3** would be prepared from carboxylic acid **4** and alcohol **5**.

Synthesis of the AB ring segment **4** is illustrated in Scheme 2. The alcohol **6**, prepared by a known procedure,[2c,e] was converted to TES ether **7** in quantitative yield. Hydrogenation and debenzylation of **7** were performed with $H_2/Pd(OH)_2$–C to give **8**. The resulting diol was protected with TIPSOTf/2,6-lutidine to give **9** in 71% overall yield. Reduction of the ester **9** with $LiAlH_4$ afforded alcohol **10** which was subjected to stepwise oxidation to furnish the carboxylic acid **4**.[4]

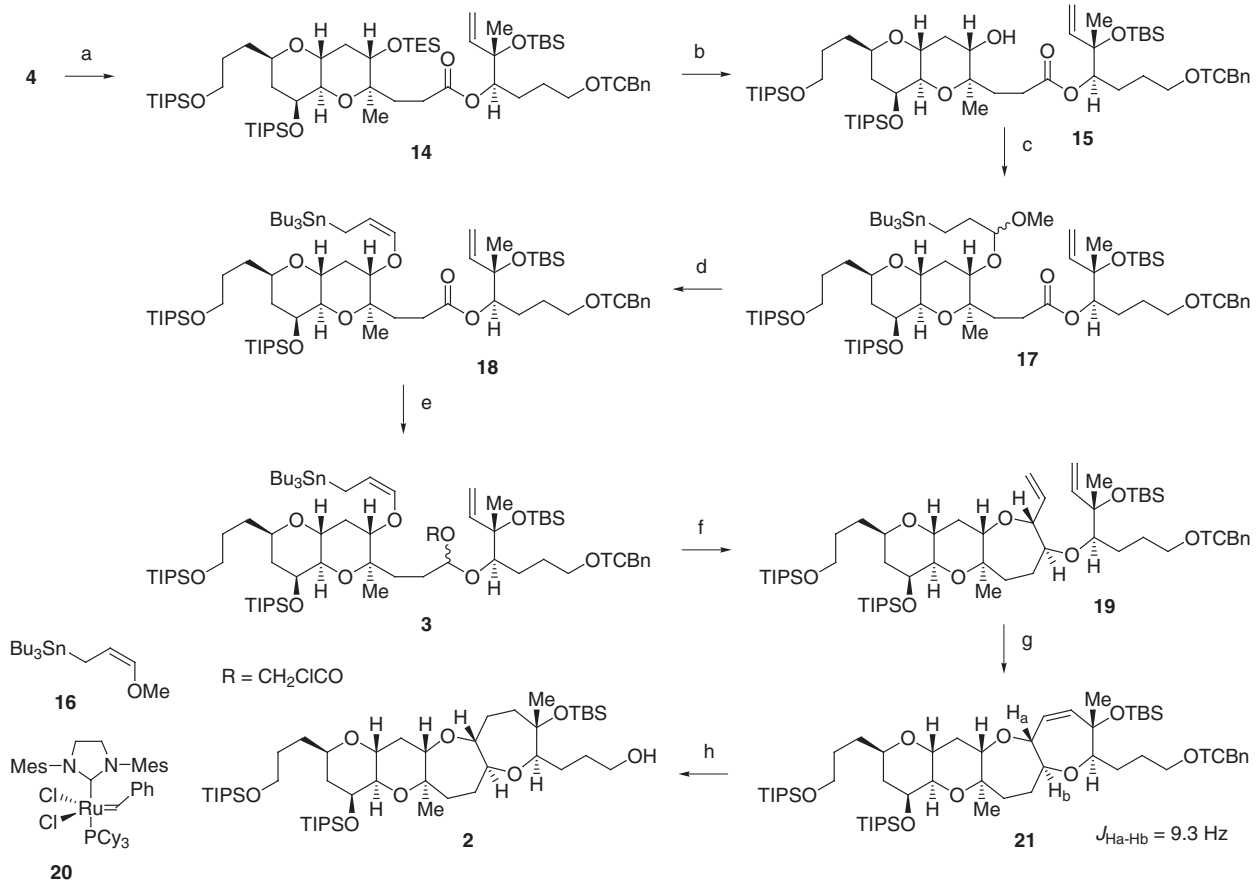
The D ring precursor **5** was prepared from the known epoxide **11** (Scheme 3). Protection of **11**[2j] with MPMCl/NaH gave **12** in 70% yield. Treatment of the epoxide **12** with dimethylsulfonium methylide generated in situ afforded allylic alcohol **13** in 77% yield.[5] Protection of the resulting tertiary alcohol with TBSOTf/2,6-lutidine followed by removal of the MPM protection provided the alcohol **5** in 61% yield.



Scheme 3. Reagents and conditions: (a) MPMCl, NaH, TBAI, THF, reflux, 70%; (b) $Me_3S^+I^-$, *n*-BuLi, THF, −10 °C to rt, 77% and (c) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C–rt, 87%; (ii) DDQ, CH_2Cl_2, aq $NaHCO_3$, 35 °C, 70%.

Coupling of the prepared segments is described in Scheme 4. Esterification of the carboxylic acid **4** and the alcohol **5** under Yamaguchi conditions gave ester **14** in 81% overall yield.[6] Selective removal of the TES protective group was performed using catalytic CSA in MeOH to afford **15** in 94% yield. Acetalization of **15** with γ-methoxyallylstannane **16** in the presence of CSA afforded mixed acetal **17** in 81% yield. Treatment of **17** with TMSI/HMDS gave allylic stannane **18** in 91% yield.[7] Modified Rychnovsky acetylation of the ester **18** provided α-acetoxy ether **3** in 65% yield.[8,9] Intramolecular allylation of **3** was carried out with $MgBr_2$·OEt_2 to give **19** as a single stereoisomer in 79% yield. Ring-closing metathesis of the diene **19** with the second generation Grubbs' catalyst **20** furnished **21** in 76% yield.[10] The stereochemistry of the 7,7-system was confirmed by ^1H NMR analysis ($J_{Ha-Hb} = 9.3$ Hz). Finally, hydrogenation of the D ring olefin and deprotection of the 2,4,6-trichlorobenzyl (TCBn) group were performed with H_2/Pd–C to give the target compound **2** in 68% yield. The physical and spectroscopic data of **2** were identical with those reported previously.[2e]

In conclusion, we have achieved a convergent formal total synthesis of hemibrevetoxin B **1** via the intramolecular allylation of an α-chloroacetoxy ether and ring-closing metathesis. The longest linear sequence leading to the key synthetic intermediate **2** from mannose was 37 steps, while our previous synthesis based on a linear synthetic strategy required 49 steps.[2c,e,11] Application of the present strategy to the synthesis of other marine natural products is in progress.



Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then **5**, DMAP, toluene, rt, 81% (four steps); (b) CSA, MeOH, 0 °C, 94%; (c) **16**, CSA, CH_2Cl_2, rt, 81%; (d) HMDS, TMSI, CH_2Cl_2, 0 °C, 91%; (e) DIBAL–H, −78 °C, CH_2Cl_2, then $(CH_2ClCO)_2O$, DMAP, pyridine, −78 °C, 65%; (f) $MgBr_2{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2, 0 °C, 79%; (g) **20**, benzene, 80 °C, 76% and (h) H_2, 10% Pd–C, EtOAc, rt, 68%.

Acknowledgements

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