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Convergent synthesis of the F–K ring segment of brevetoxin B

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Abstract—A convergent synthesis of the F–K ring segment of brevetoxin B has been achieved via the intramolecular allylation of an α-chloroacetoxy ether and subsequent ring-closing metathesis.
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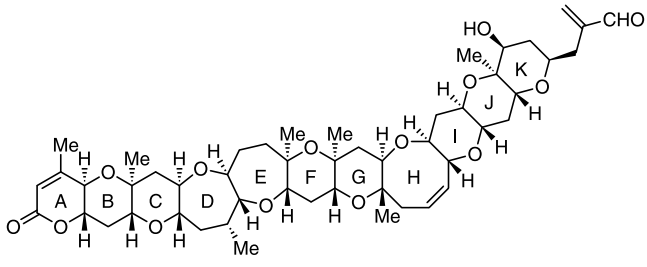
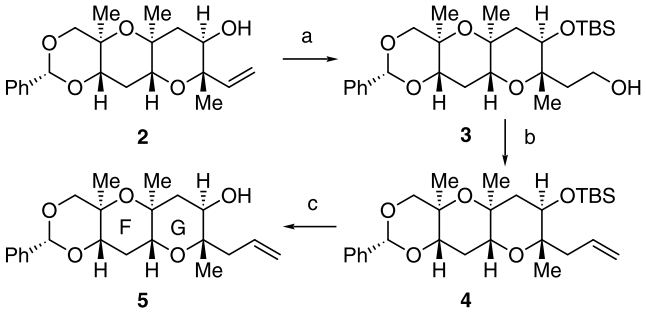
Brevetoxin B (**1**), a potent neurotoxin was isolated from the red tide organism *Gymnodinium breve* Davis in 1981 as the first example of a marine polycyclic ether.[1] The unique structural features and biological activity of this molecule have attracted the attention of synthetic chemists.[2] In 1995, the first total synthesis of **1** was achieved by Nicolaou and co-workers using a hydroxy dithioacetal cyclization for the key segment connection constructing the H ring moiety.[3] Nakata, et al. reported the second total synthesis based on the same segment coupling strategy in 2002.[4] Recently, we developed an efficient method for the convergent synthesis of polycyclic ethers via the intramolecular allylation of an α-acetoxy ether and subsequent ring-closing metathesis.[5] In this paper, we wish to report a new approach to the convergent synthesis of the F–K ring segment of **1** based on our own methodology.

Scheme 1 shows the synthesis of the FG ring segment. The known olefin **2**[2d] was converted to the alcohol **3** via TBS protection and hydroboration in 86% yield. Swern oxidation of **3** followed by Wittig reaction gave **4** in 87% yield. Treatment of the silyl ether **4** with TBAF gave the FG ring segment **5** in 90% yield.

The synthesis of the JK ring segment is illustrated in Scheme 2. Ozonolysis of the known olefin **6**[2d] afforded the corresponding aldehyde, which was subjected to the Barbier type allylation using allyl bromide and Zn powder in the presence of satd NH_4Cl to give a 2:1 mixture of the desired homoallylic alcohol **7** and its stereoisomer **8** in 93% combined yield.[6,7] Ozonolysis of





Scheme 1. *Reagents and conditions*: (a) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 97%; (ii) 9-BBN, THF, rt, then 3N NaOH, 30% H_2O_2, 0°C, 89%; (b) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, −78°C to rt; (ii) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0°C, 87% (two steps); (c) TBAF, THF, rt, 90%.

Keywords: brevetoxin B; polycyclic ethers; convergent synthesis.
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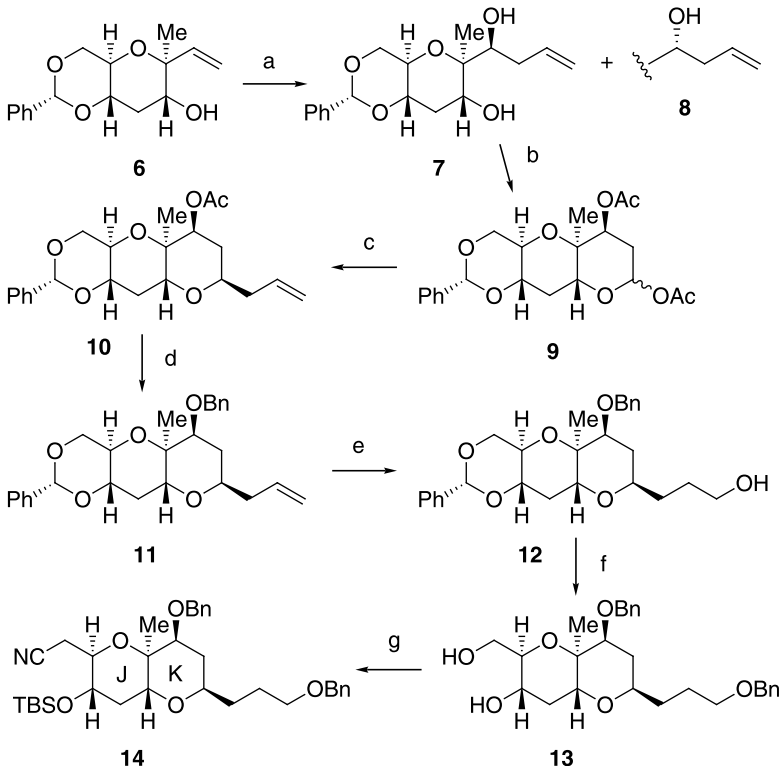

Scheme 2. *Reagents and conditions*: (a) (i) O_3, MeOH, −78°C, then Me_2S; (ii) allyl bromide, Zn powder, satd NH_4Cl, THF, 0°C, 93% (two steps, **7**:**8** = 2:1); (b) (i) O_3, CH_2Cl_2, −78°C, then PPh_3; (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, reflux, 97% (two steps); (c) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_3CN, 0°C, 65%; (d) (i) NaOMe, MeOH, rt, 98%; (ii) BnBr, KH, THF, rt, 100%; (e) 9-BBN, THF, rt, then 30% H_2O_2, 3N NaOH, 0°C, 96%; (f) (i) BnBr, KH, THF, rt; (ii) CSA, MeOH, rt, 95% (two steps); (g) (i) TsCl, Et_3N, CH_2Cl_2, reflux, 89%; (ii) NaCN, DMSO, 50°C, 100%; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 100%.

7 followed by acetylation of the resulting hemiacetal gave **9** in 97% yield. Treatment of **9** with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ gave **10** as the sole product in 65% yield. Removal of the acetyl group followed by benzyl protection of the resulting alcohol afforded **11** in quantitative yield. Hydroboration of **11** gave the alcohol **12** in 96% yield. Benzyl protection followed by hydrolysis of the benzylidene acetal provided the diol **13** in 95% yield. Selective tosylation of the primary alcohol, treatment with sodium cyanide, and TBS protection of the remaining secondary alcohol gave the JK ring segment **14** in 89% yield.

Scheme 3 describes the coupling of the FG and JK ring segments. DIBAL-H reduction of **14** followed by oxidation of the resulting aldehyde with $NaClO_2$ gave the carboxylic acid **15**, which was subjected to the Yamaguchi esterification[8] with the alcohol **5** to give the ester **16** in 55% yield. Desilylation of the TBS group of **16** with TBAF, acid catalyzed reaction of **17** with **18** gave the mixed acetal **19**. Subsequent acetal cleavage with TMSI/HMDS furnished the allylic stannane **20** in 73% yield.[9] Modified Rychnovsky acetylation including the partial reduction of **20** with DIBAL-H followed by trapping of the resulting aluminum hemiacetal with chloroacetic anhydride gave the cyclization precursor **21** in quantitative yield.[10,11] Intramolecular allylation of **21** was carried out using $BF_3{\cdot}OEt_2$ to afford **22** as a single stereoisomer in 75% yield. Finally, the diene **22** was subjected to ring-closing metathesis using the second generation Grubbs catalyst **23**[12] to furnish the F–K ring framework **24** in 91% yield. The *trans* relationship between Ha and Hb was confirmed by the large coupling constant, $J_{Ha\text{-}Hb} = 8.5$ Hz.

In conclusion, we have achieved the convergent synthesis of the F–K ring segment of brevetoxin B (**1**) via the intramolecular allylation of α-chloroacetoxy ether **21** and subsequent ring-closing metathesis. Further studies toward the total synthesis of **1** are now in progress in our laboratories.

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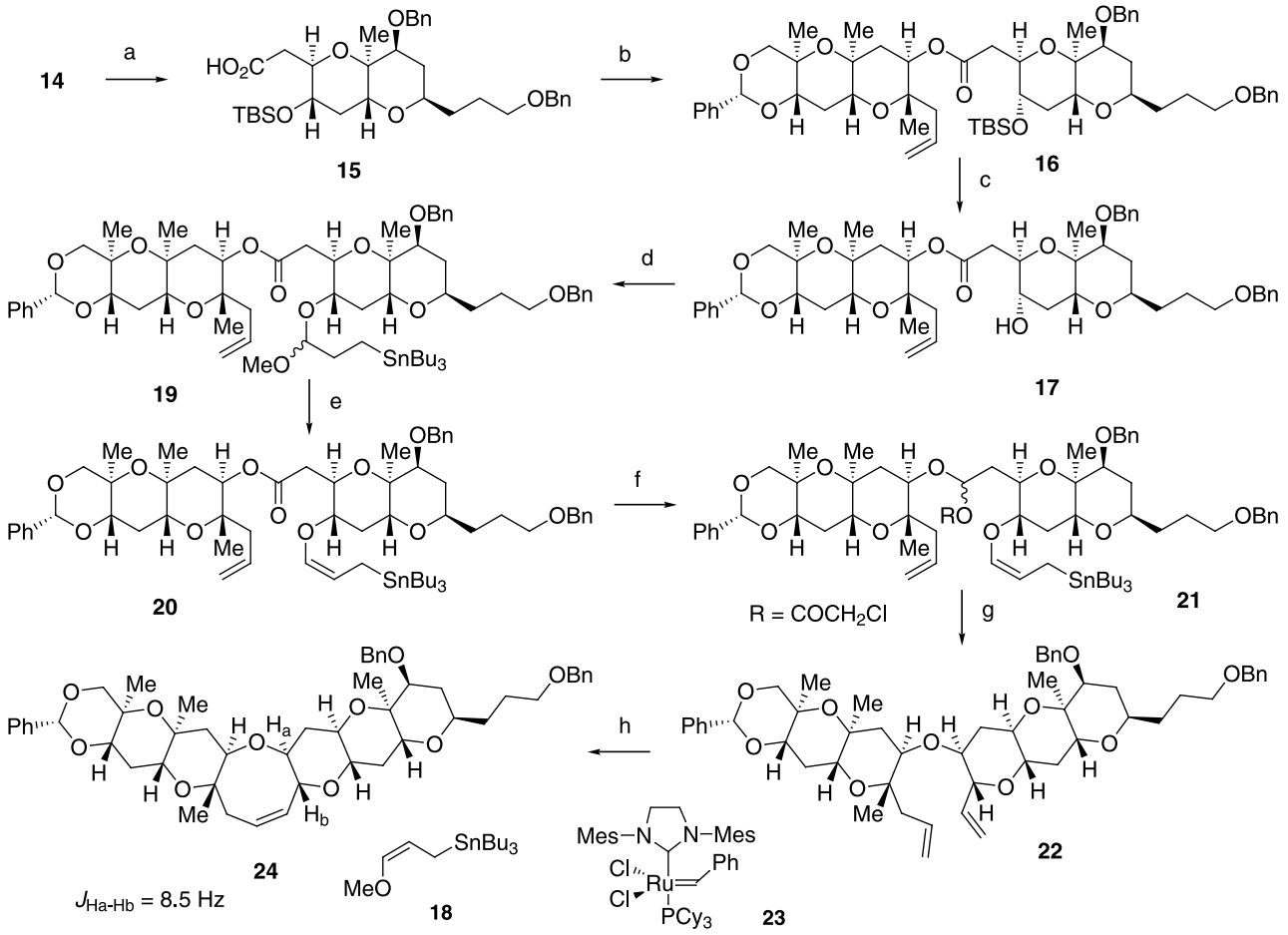

Scheme 3. *Reagents and conditions*: (a) (i) DIBAL-H, CH_2Cl_2, −78°C, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/THF/H_2O, rt; (b) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then **5**, DMAP, toluene, rt, 55% (three steps); (c) TBAF, THF, rt, 96%; (d) **18**, CSA, CH_2Cl_2, rt, 95%; (e) TMSI, HMDS, CH_2Cl_2, 0°C, 83%; (f) DIBAL-H, CH_2Cl_2, −78°C, then $(CH_2ClCO)_2O$, pyridine, DMAP, −78°C, 100%; (g) $BF_3{\cdot}OEt_2$, CH_3CN–CH_2Cl_2 (20:1), −45 to 0°C, 75%; (h) **23**, CH_2Cl_2, rt, 91%.

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