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A cross-metathesis approach to the stereocontrolled synthesis of the AB ring segment of ciguatoxin

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Abstract

Synthesis of the AB ring segments of ciguatoxin is described. The present synthesis includes a Lewis acid mediated cyclization of allylstannane with aldehyde, cross-metathesis reaction introducing the side chain, and Grieco–Nishizawa dehydration on the A ring.

Keywords: Ciguatoxin; Polycyclic ethers; Allylstannane–aldehyde condensation; Cross-metathesis

Ciguatoxin (**1**), a principal causative toxin of 'ciguatera' seafood poisoning, was isolated from moray eel *Gymnothorax javanicus*.[1] The potent neurotoxicity and novel polycyclic ether framework including five- to nine-membered rings have attracted the attention of synthetic chemists.[2,3] The first total synthesis of **1** was achieved by Inoue and Hirama in 2006.[4] As well as the construction of the huge molecular architecture, synthesis of the labile dihydroxybutenyl substituent on the A ring moiety is a great synthetic challenge.[5] In this Letter, we describe a stereocontrolled synthesis of the AB ring segment of ciguatoxin (**1**) via a cross-metathesis reaction.[6]

Scheme 1 illustrates our synthetic strategy. The AB ring segment **2** is retrosynthetically broken down into the side chain moiety **3** and bicycle **4**. The 6–7 ring system **4** would be constructed from **5** via an intramolecular reaction of allylstannane with aldehyde. The vinyl group of **4**, generated by the cyclization process, can be a suitable substrate for the subsequent cross-metathesis. The cyclization precursor **5** can be prepared from the known compound **6**.

As a preliminary study, we examined the synthesis of a 1,4-diene system by using the simple substrate **7**[7] via the Grieco–Nishizawa protocol. Thus, the treatment of **7** with 2-nitro-phenylselenocyanate/Bu_3P afforded alkyl selenide **8** via S_N2 stereoinversion (Scheme 2). Oxidation of **8** with H_2O_2 gave selenoxide intermediate **9**, which immediately underwent *syn*-elimination to furnish **10** as the sole product in 88% overall yield.[8,9] Although the desired 1,4-diene was obtained in good yield, however, the reaction with the olefin **11**[10] using metathesis catalyst such as the second generation Grubbs catalyst **12**[11] gave poor result. Only a trace amount of the desired product **13** was detected in the reaction mixture.[12]

After several unfruitful attempts, we found that the cross-metathesis of **7** and **11** in the presence of catalyst **12** proceeded to give product **14** in reasonable yield (Scheme 3). Alcohol **14** was then dehydrated to give 1,4-diene **13** in 54% yield.[13,14]

Encouraged by these results, we next investigated the synthesis of the AB ring segment **2**. Protection of the known alcohol **15**[15] as an ethoxyethyl ether followed by hydroboration–oxidation provided the corresponding primary alcohol, which was treated with CSA in MeOH giving diol **16** in 81% overall yield (Scheme 4). Selective protection of the primary hydroxyl group with TBDPSCl/imidazole afforded **17** in quantitative yield. Treatment of the secondary alcohol with the γ-methoxy-allylstannane **18** gave the

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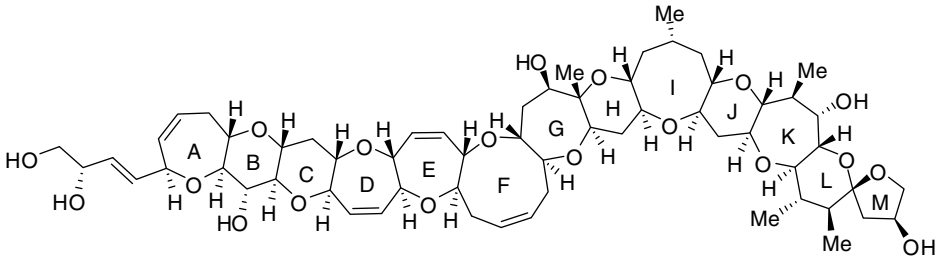
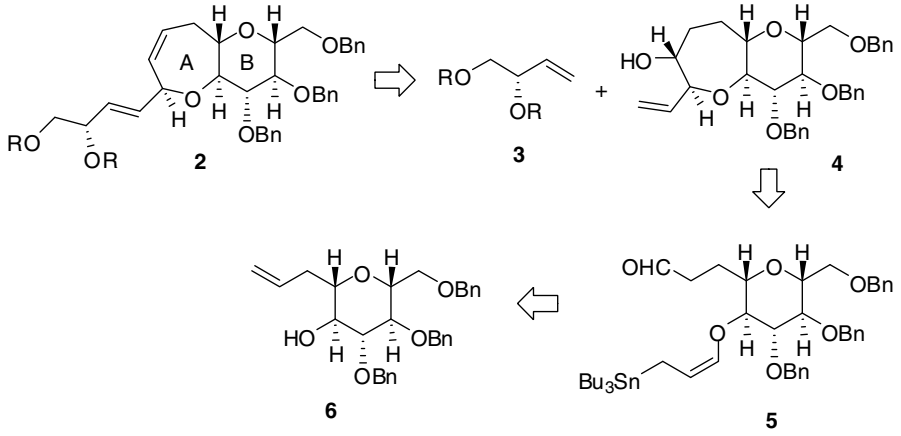
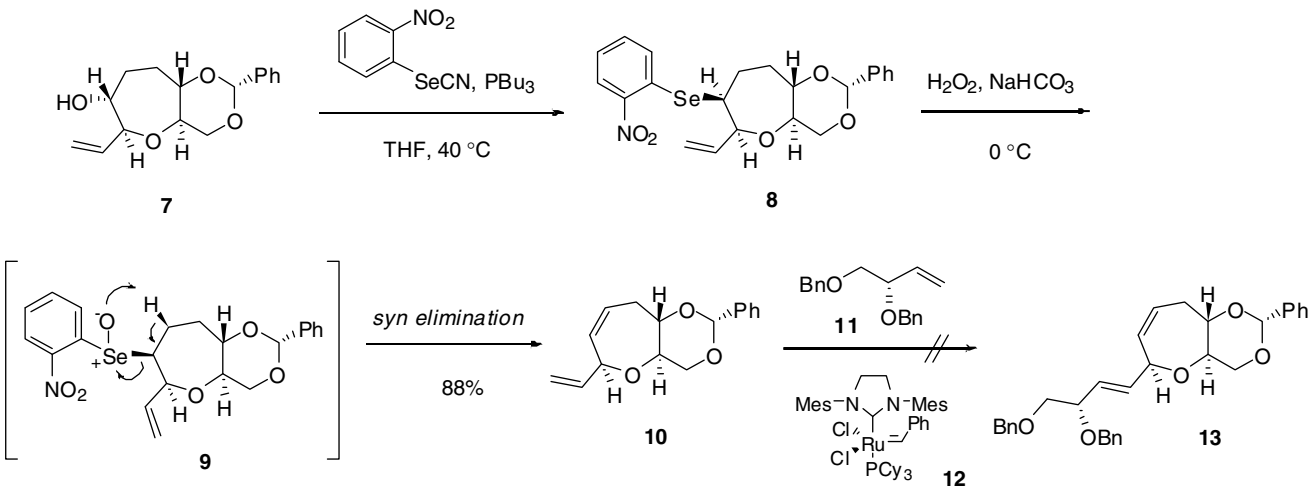


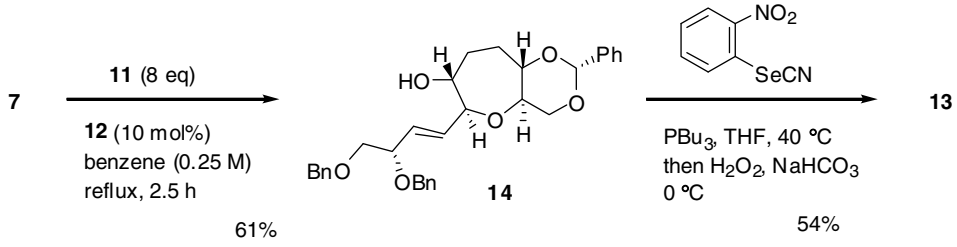
Ciguatoxin (**1**)



Scheme 1.



Scheme 2.



Scheme 3.