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

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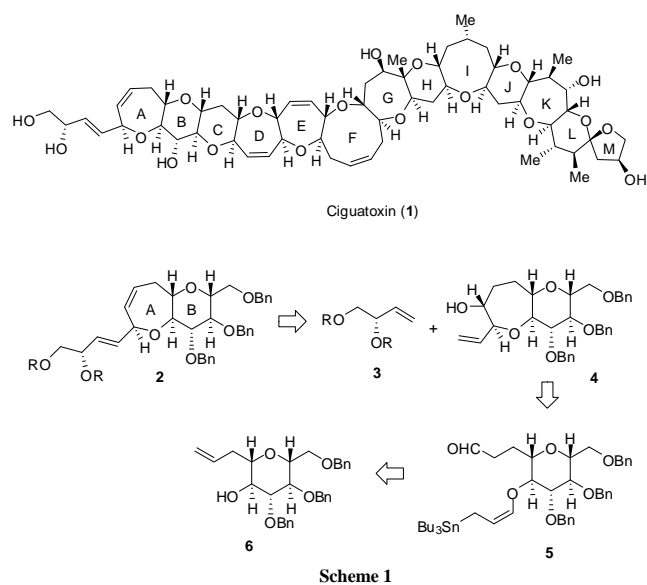
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Abstract— Synthesis of the AB ring segments of ciguatoxin is described. The present synthesis includes a Lewis acid mediated cyclization of allylstannane with aldehyde, cross-metathesis reaction introducing the side chain, and Grieco-Nishizawa dehydration on the A ring. © 2008 Elsevier Science. All rights reserved

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 Hiramatsu 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 paper, we describe a stereocontrolled synthesis of the AB ring segment of ciguatoxin (**1**) via a cross-metathesis reaction.⁶

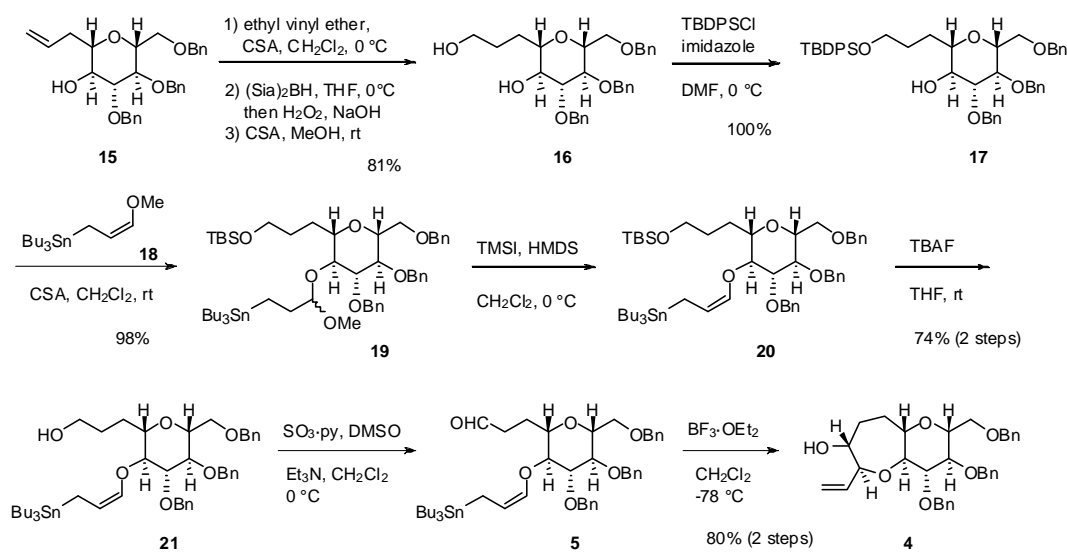
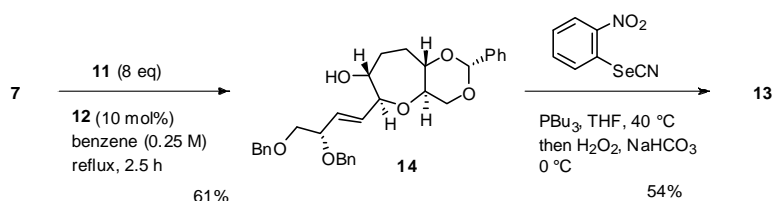
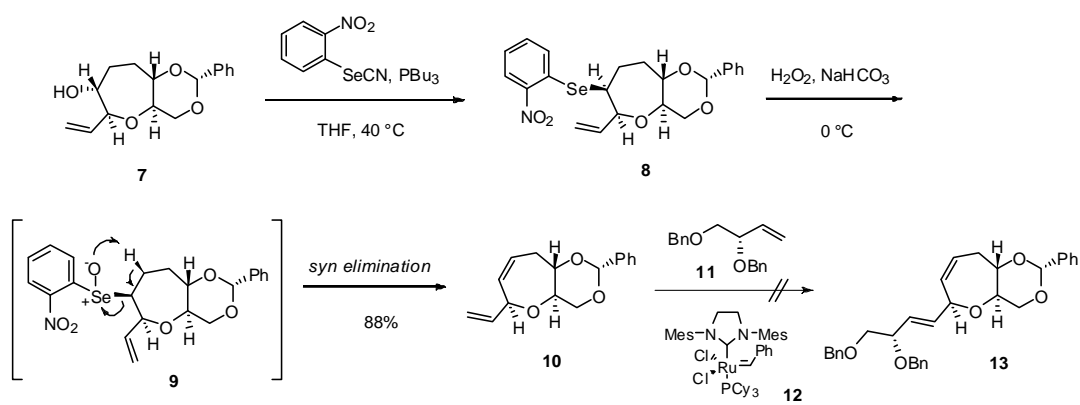


Scheme 1 illustrates our synthetic strategy. The AB ring segment **2** is retrosynthetically broken down into the side chain moiety **3** and the bicyclic **4**. The 6-7 ring system **4** would be constructed from **5** via an intramolecular reaction of allylstannane with aldehyde. The vinyl group of **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** via the Grieco-Nishizawa protocol. Thus, treatment of **7** with 2-nitro-phenylselenocyanate/ Bu_3P afforded alkyl selenide **8** via $\text{S}_{\text{N}}2$ 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 the catalyst **12** proceeded to give the product **14** in reasonable yield (Scheme 3). The alcohol **14** was then dehydrated to give the 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

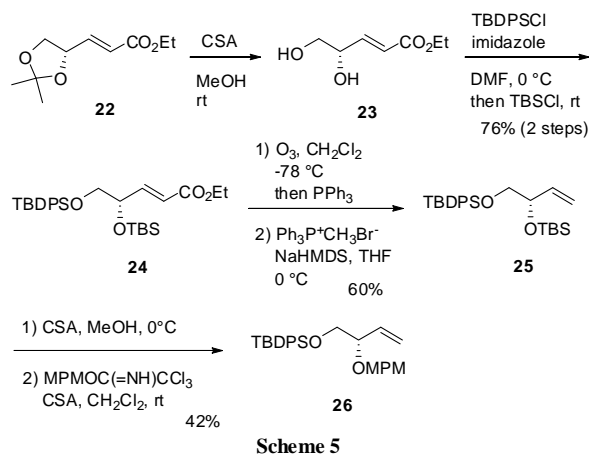


hydroboration-oxidation provided the corresponding primary alcohol, which was treated with CSA in MeOH giving the diol **16** in 81% overall yield (Scheme 4). Selective protection of the primary hydroxyl group with TBDPSCI/imidazole afforded **17** in quantitative yield. Treatment of the secondary alcohol with the γ -methoxyallylstannane **18** gave the mixed acetal in 98% yield. Acetal cleavage of **19** was performed using TMSI/HMDS to give the allylic stannane **20**,¹⁶ which was treated with TBAF furnishing **21** in 74% overall yield. Oxidation of the primary alcohol with $\text{SO}_3\cdot\text{py}/\text{DMSO}/\text{Et}_3\text{N}$ gave the

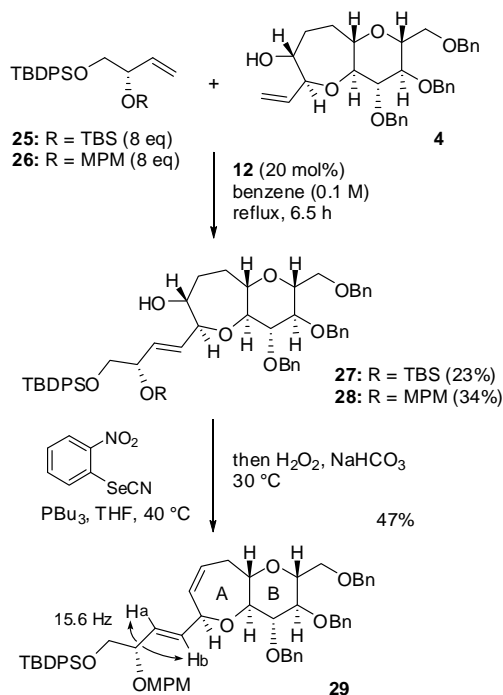
aldehyde **5**, which was then subjected to the $\text{BF}_3\cdot\text{OEt}_2$ mediated cyclization to afford the bicyclic compound **4** as a single stereoisomer in 80% overall yield.¹⁷⁻¹⁹ The cyclization product **4** having a vinyl group can be used directly for the next cross-metathesis reaction.

Preparation of the chiral side chain segment is described in Scheme 5. Hydrolysis of the acetonide **22**, prepared from D-mannitol,²⁰ gave the corresponding diol **23**, which was treated with TBDPSCI/imidazole followed by TBSCl to

afford **24** in 76% overall yield. Ozonolysis of the alkene **24**, followed by Wittig reaction of the resulting aldehyde furnished **25** in 60% overall yield. The side chain segment **26** having a MPM group was prepared via selective removal of the TBS group followed by protection of the resulting alcohol as a MPM ether in 42% overall yield.



Both of the substrates were in hand, we next examined the cross-metathesis (Scheme 6). Treatment of **4** with **25** (8 eq) in the presence of the catalyst **12** (20 mol%) provided **27** as a single stereoisomer in 23% yield. The yield was slightly improved by using the less hindered substrate **26**, and the product **28** was obtained in 34% yield. Finally, the alcohol **28** was subjected to the Grieco-Nishizawa protocol to furnish the AB ring segment **29** in 47% yield. The coupling constants, $J_{\text{Ha-Hb}} = 15.6$ Hz, clearly indicated the *E*-geometry of the side chain olefin.



In conclusion, the stereocontrolled synthesis of the AB ring segment of ciguatoxin was achieved. The Lewis acid mediated allylstannane-aldehyde condensation was successfully applied to the synthesis of the seven-membered cyclic ether skeleton. Cross-metathesis and subsequent Grieco-Nishizawa dehydration protocol were effective for the construction of the 1,4-diene system. Further studies towards the total synthesis of ciguatoxin are in progress in our laboratories.

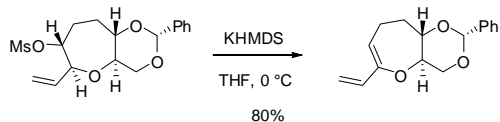
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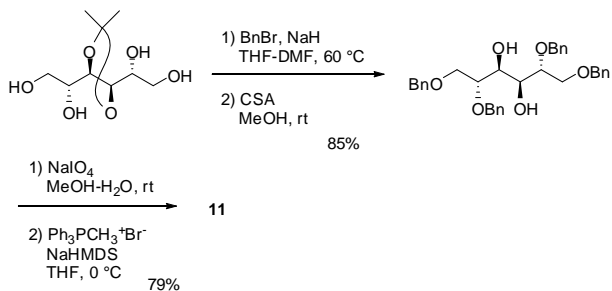
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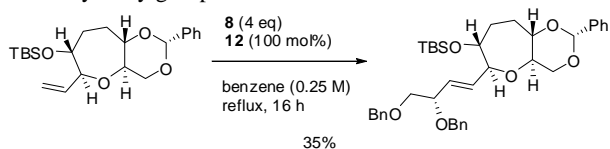
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9. Treatment of the mesylate, prepared from **7**, with KHMDS afforded the undesired 1,3-diene derivative as the sole product.



10. The olefin **8** was prepared as follows.



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12. Similar problem of the cross-metathesis with a 1,4-diene derivative was reported by Hirma, see ref. 5f.
13. Protection of the hydroxy group of **7** as a TBS ether inhibited the cross-metathesis. The reaction was very slow even in the presence of 1 equivalent of **12**, and the product was obtained in 35% yield after 16 h as shown below. One of the referee suggested carrying out this reaction to clarify the effect of the free hydroxy group on the cross-metathesis.



14. Recently, the acceleration effect of allylic hydroxy group on ring-closing enyne metathesis was reported, see: Imahori, T.; Ojima, H.; Takeyama, H.; Mihara, Y.; Takahata, H. *Tetrahedron Lett.* **2008**, *49*, 265-268.
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18. Construction of the A ring moiety via the allylstannane-aldehyde condensation has been investigated by Hirma, see ref. 5b, c.
19. The stereochemistry of the product **20** was confirmed by ¹H NMR analysis as shown below.

