Chemistry

Organic Chemistry fields

Okayama University *Year* 2008

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

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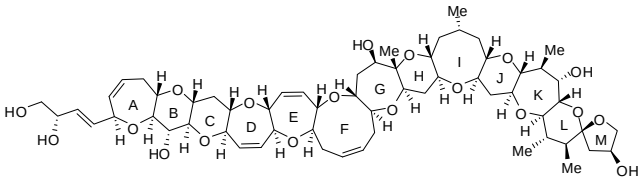
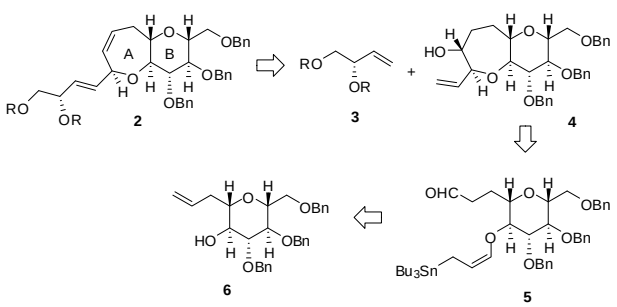
Keywords: ciguatoxin, polycyclic ethers, allylstannane-aldehyde condensation, cross-metathesis.

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.

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



Ciguatoxin (**1**)



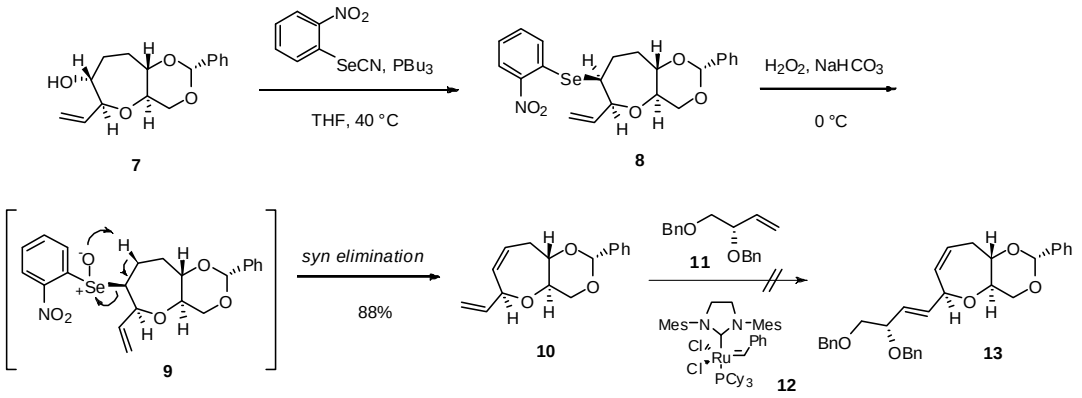
Scheme 1

Scheme 1 illustrates our synthetic strategy. The AB ring segment **2** is retrosynthetically broken down into the side chain moiety **3** and the bicycle **4**. The 6-7 ring system **4** would be constructed from **5** via an intramolecular reaction of allylstannnane 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**.

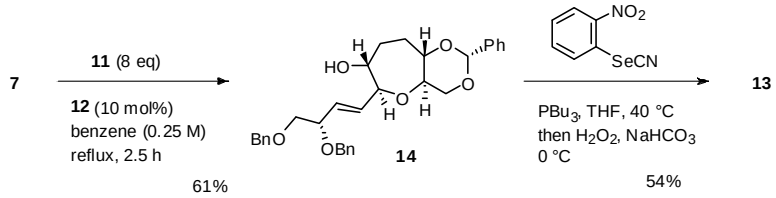
As a preliminary study, we examined the synthesis of a 1,4-diene system by using the simple substrate **7**[7] via the Grieco-Nishizawa protocol. Thus, treatment of **7** with 2-nitro-phenylselenocyanate/Bu_3P afforded alkyl selenide **8** via S_N2 stereoinversion (Scheme 2). Oxidation of **8** with 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 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]

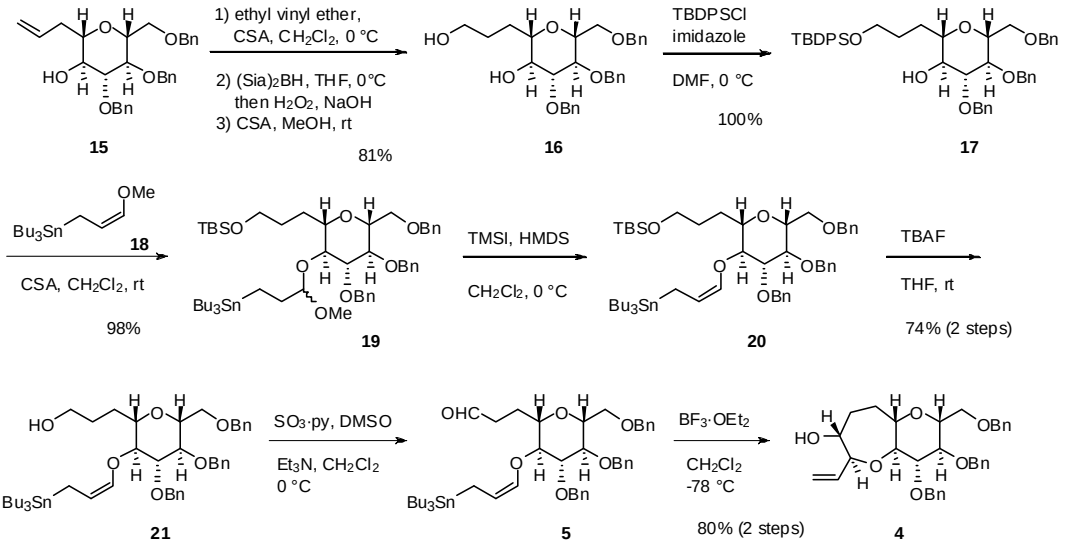
Encouraged by these results, we next investigated the synthesis of the AB ring segment **2**. Protection of the known alcohol **15**[15] as an ethoxyethyl ether followed by



Scheme 2



Scheme 3

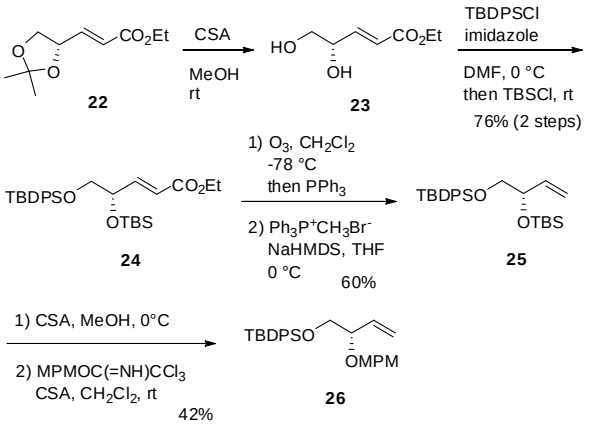


Scheme 4

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 TBDPSCl/imidazole afforded **17** in quantitative yield. Treatment of the secondary alcohol with the γ-methoxy-allylstannane **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 SO_3·py/DMSO/Et_3N gave the aldehyde **5**, which was then subjected to the BF_3·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.

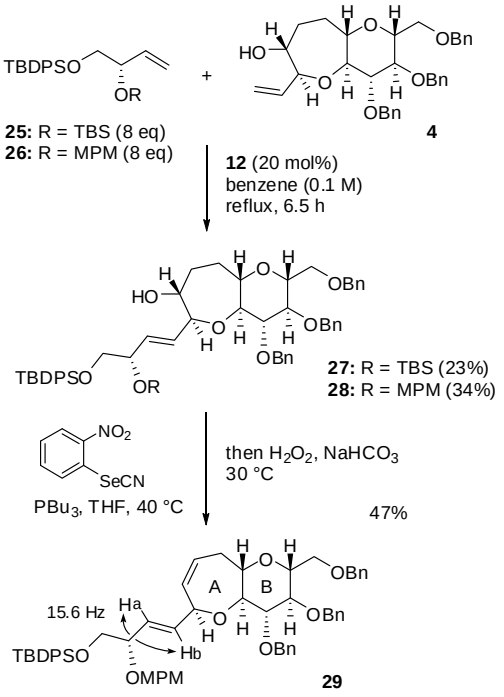
Preparation of the chiral side chain segment is described in Scheme 5. Hydrolysis of the acetonide **22**, prepared from D-mannitol,[20] gave the corresponding diol **23**, which was treated with TBDPSCl/imidazole followed by TBSCl to

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.



Scheme 5

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, $J_{Ha\text{-}Hb}$ = 15.6 Hz, clearly indicated the *E*-geometry of the side chain olefin.



Scheme 6

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.

Acknowledgement

This work was financially supported by the Nagase Science and Technology Foundation, and the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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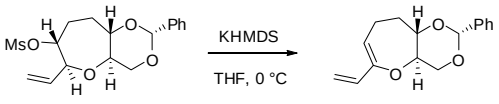
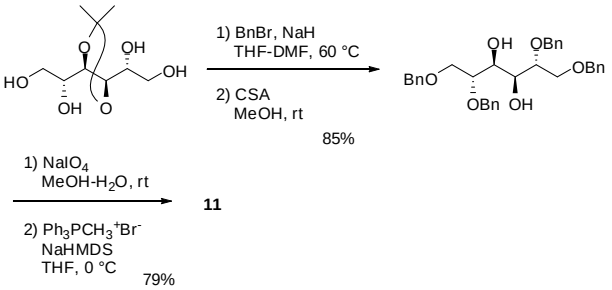
9. Treatment of the mesylate, prepared from **7**, with KHMDS afforded the undesired 1,3-diene derivative as the sole product.



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



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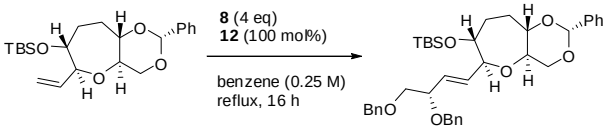
12. Similar problem of the cross-metathesis with a 1,4-diene derivative was reported by Hirama, see ref. 5f.
13. Protection of the hydroxy group of **7** as a TBS ether inhibited the closs-metathesis. The reaction was very slow even in the presence of 1 equivalent of **12**, and the product was obtained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



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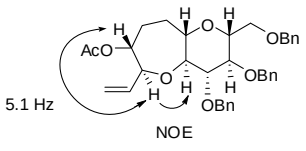
18. Construction of the A ring moiety via the allylstannane-aldehyde condensation has been investigated by Hirama, see ref. 5b, c.
19. The stereochemistry of the product **20** was confirmed by ^{1}H NMR analysis as shown below.



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