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Convergent synthesis of the EFGH ring system of ciguatoxin CTX3C

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ABSTRACT

Convergent synthesis of the EFGH ring segment of ciguatoxin CTX3C was investigated by using the intramolecular allylation of an α-chloroacetoxy ether and/or *O,S*-acetal, and subsequent ring-closing metathesis. A new method for the preparation of γ-alkoxyallylstannane is also described.

1. Introduction

Ciguatoxin CTX3C (**1**),[1] one of the causative toxin of 'ciguatera' seafood poisoning,[2] was isolated from cultured dinoflagellate *Gambierdiscus toxicus*. Due to the potent neurotoxicity and novel polycyclic ether framework including five-to nine-membered rings, CTX3C (**1**) has attracted the attention of synthetic chemists.[3] In 2001, Hirama and co-workers reported the first total synthesis of **1** by using a radical cyclization followed by ring-closing metathesis for the final key segment coupling.[4] Previously, we developed a method for the convergent synthesis of polycyclic ethers via the intramolecular allylation and ring-closing metathesis.[5] Based on this methodology, we planned a convergent synthesis of **1**, and have achieved the synthesis of the A–E ring segment **2**[6] and H–M ring segment **3**[7] (Scheme 1). In this paper, we wish to describe a convergent synthesis of the EFGH ring system of ciguatoxin CTX3C (**1**) as a model study for the coupling of the A–E and H–M ring segments based on our own methodology. Fig. 1.

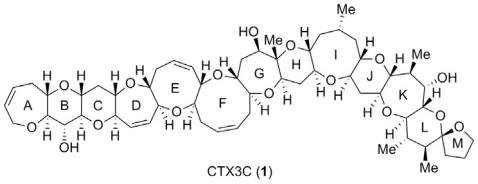

Fig. 1. Structure of ciguatoxin CTX3C(**1**).

2. Results and discussion

2.1. First generation retrosynthetic analysis

Our retrosynthetic analysis of the model compound **4** is illustrated in Scheme 2. The FG ring moiety of **4** would be constructed by the intramolecular allylation followed by ring-closing metathesis of α-acetoxy ether **5** via intramolecular allylation and suitable chain elongation followed by ring-closing metathesis. The cyclization precursor **5** was broken down into the E and H ring segment, **6** and **7**.

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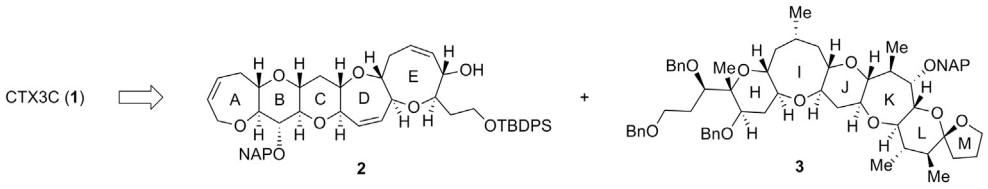
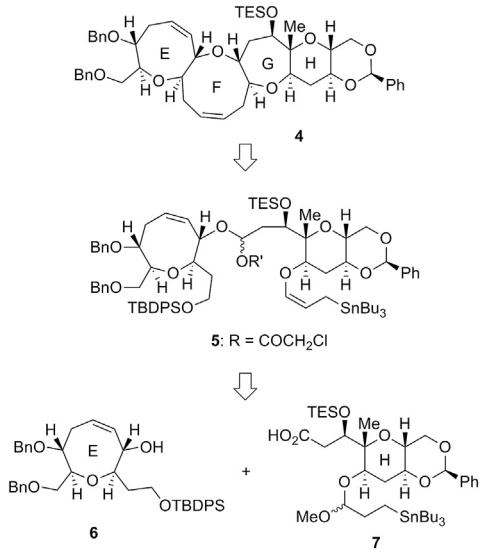


Scheme 1. Retrosynthetic analysisi of **1**.



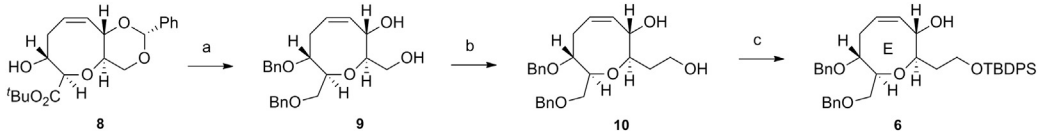
Scheme 2. Retrosynthetic analysis of the EFGH ring system **4**.

2.2. Preparation of the E ring segment 6

Scheme 3 describes the synthesis of the E ring segment **6**. Reduction of the known ester **8**[6a,8] with DIBAL-H, protection of the resulting diol with BnBr/NaH followed by removal of the benzylidene with CSA gave diol **9** in 43% overall yield. Selective tosylation of the primary alcohol of **9** with TsCl/Et_3N followed by the reaction with NaCN provided the corresponding nitrile, which was subjected to stepwise reduction with DIBAL-H and $NaBH_4$ to give diol **10** in 31% overall yield. Selective protection of the primary alcohol of **10** was carried out with TBDPSCl/imidazole to furnish the E ring segment **6** in quantitative yield.

secondary alcohol **13** was reacted with **14** in the presence of catalytic CSA to afford mixed acetal **15** in 41% yield along with a significant amount of unreacted **13**. Reductive removal of the acetyl groups of **15** with DIBAL-H, protection of the resulting diol with TESOTf/2,6-lutidine, and selective removal of the primary TES group with catalytic PPTS gave **16** in 73% overall yield. Stepwise oxidation of the primary alcohol **16** was performed with TPAP/NMO followed by $NaClO_2/NaH_2PO_4$ to give the carboxylic acid **7**, which was used directly to the esterification with the E ring alcohol **6** under the Yamaguchi conditions to furnish ester **17** in 73% overall yield.[12] Treatment of **17** with TMSI/HMDS provided allylic stannane **18** in 81% yield.[13] The ester **18** obtained was then subjected to the modified Rychnovsky reductive acetylation.[14,15] However, unfortunately, several attempts resulted in failure to obtain the desired compound **5**. Presumably, steric repulsion between TES group and isobutyl group would destabilize the aluminum hemiacetal intermediate, and would promote the over-reduction to cleave the ester group.[16,17]

We next examined the further transformation with smaller protective group, a MOM ether (Scheme 5). Removal of the TES group of **18** with TBAF, and subsequent protection with MOMCl/^{i}Pr$_2$NEt provided **19** in 47% overall yield. The modified Rychnovsky reductive acetylation of **19** proceeded smoothly to afford the desired α-acetoxy ether **20**.[14,15] Intramolecular allylation of **20** was carried out with $BF_3\cdot OEt_2$ to give cyclized product **21** as a single stereoisomer in 64% overall yield. The *trans* relationship between Ha and Hb of **21** was confirmed by the coupling constant, $J_{Ha\text{-}Hb}$=0 Hz.[18] Selective hydroboration of the terminal olefin of **21** was performed with 9-BBN followed by oxidative workup leading to **22** in 70% yield. Oxidation of the primary alcohol of **22** with $SO_3\cdot$py/DMSO/Et_3N followed by Wittig reaction provided the corresponding alkene. Removal of the TBDPS group with TBAF, oxidation with $SO_3\cdot$py/DMSO/Et_3N followed by Wittig reaction furnished **23** in 78% overall yield. Finally, ring-closing metathesis of **23** was performed with the Grubbs catalyst **24** to furnish the EFGH ring seg-



Scheme 3. *Reagents and conditions*: (a) (i) DIBAL-H, CH_2Cl_2, −78 °C, 61%; (ii) BnBr, NaH, TBAI, THF, reflux, 97%; (iii) CSA, MeOH−CH_2Cl_2, 40 °C, 72% (99% based on recovery); (b) (i) TsCl, Et_3N, CH_2C1_2, reflux, 40% (94% based on recovery); (ii) NaCN, DMSO, 70 °C, 99%; (iii) DIBAL-H, CH_2C1_2, −78 °C; (iv) $NaBH_4$, MeOH, −78 to 0 °C, 77% (2 steps); (c) TBDPSCl, imidazole, DMF, rt, quant.

2.3. Coupling of the E and H ring segments

The initial attempt at the segment coupling is illustrated in Scheme 4. After protection of the known alcohol **11**[9] with MOMCl/^{i}Pr$_2$NEt, the ester was reduced with DIBAL-H, and the resulting allylic alcohol was subjected to the Sharpless asymmetric epoxidation to provide epoxy alcohol **12** as a single stereoisomer in 88% overall yield.[10] Reductive cleavage of the epoxide **12** was carried out with Red-Al,[11] protection of the resulting diol with Ac_2O/pyridine, and removal of the MOM protection with TMSI/HMDS gave **13** in 88% overall yield. The

ment **25** in 73% yield.[19] The stereochemistry of **25** was unambiguously confirmed by conversion to a known compound **26**. Thus, removal of the acetal protective groups of **25** with catalytic CSA followed by protection with NaH/BnBr provided **26** in 85% overall yield. The spectroscopic data of **26** obtained are identical with those reported previously.[20]

Although the convergent synthesis of the EFGH ring system of CTX3C (**1**) was achieved as described, there is a room for improvement. Particularly, the low conversion of the acetalization of **13** with **14** (Scheme 4) would become a problem for the coupling of the huge A–E and H–M ring segments.