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IMPROVDED SYNTHESIS OF THE A-E RING SEGMENT OF CIGUATOXIN CTX3C

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Dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

Abstract – The improved synthesis of the A-E ring segment of ciguatoxin CTX3C was performed via a highly convergent approach based on intramolecular allylation-RCM methodology.

Ciguatoxin CTX3C (**1**),[1] one of the causative toxin of "ciguatera" seafood poisoning, was isolated from cultured dinoflagellate *Gambierdiscus toxicus* (Figure 1).[2] The unique structural features and potent neurotoxicity of this molecule have attracted significant attention of synthetic chemists.[3,4] Herein, we wish to describe the improved synthesis of the A-E ring segment of ciguatoxin CTX3C as a part of the synthetic study of **1**.

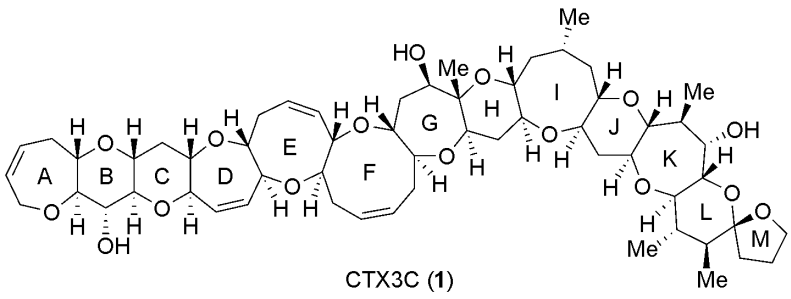
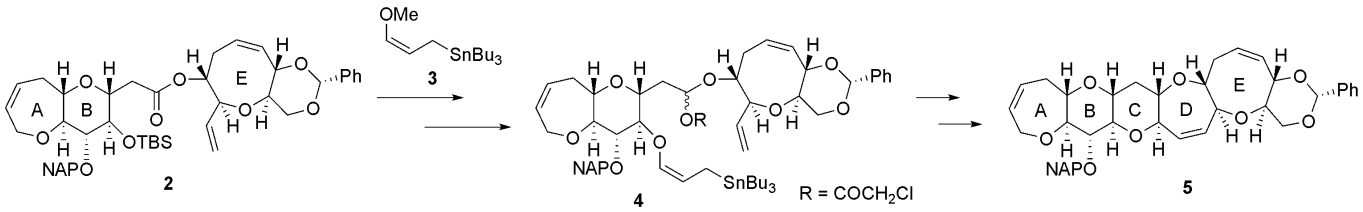


Figure 1. Structure of ciguatoxin CTX3C (**1**)

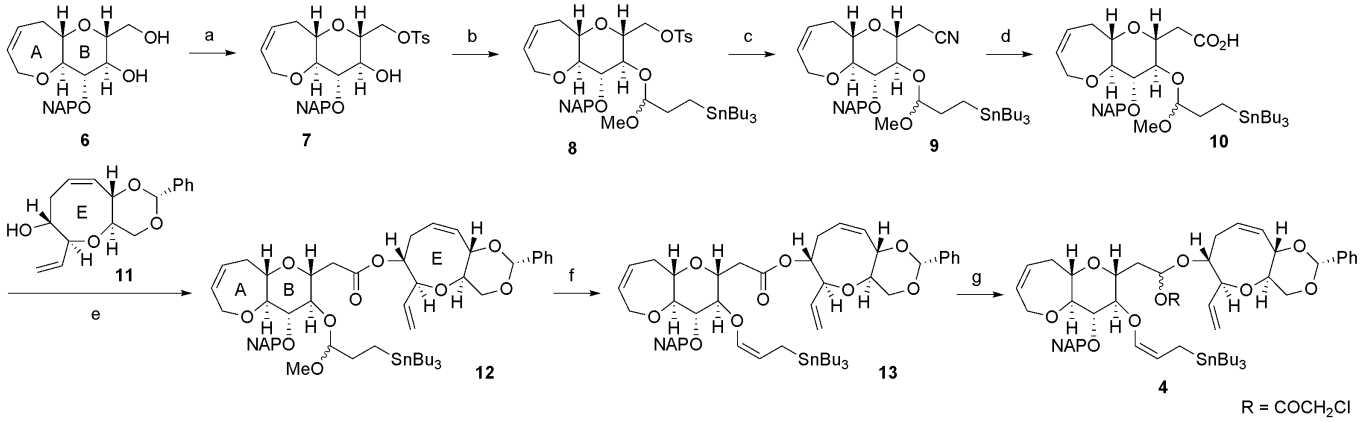
Previously, we reported the convergent synthesis of A-E ring segment of **1** as shown in Scheme 1.[5,6] The ester **2**, prepared from an AB ring carboxylic acid and E ring alcohol, was converted to α-chloroacetoxy ether **4** via the reaction with γ-methoxyallylstannane **3**. The intramolecular allylation

of **4** followed by ring-closing metathesis provided the A-E ring segment **5**.[7] In this paper, we wish to describe the improved synthesis of the A-E ring segment having a suitable side chain for the construction of the F ring moiety.



Scheme 1

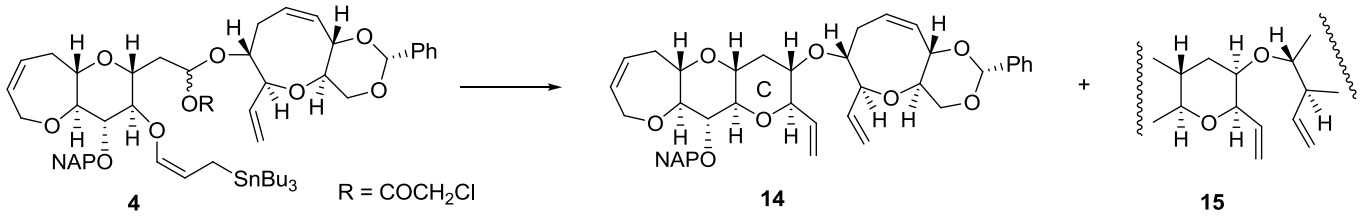
To improve the efficiency of the synthesis, we planed to perform the reaction of **3** with the AB ring moiety before the segment coupling. Selective tosylation of known diol **6**[6b] with TsCl/pyridine gave monotosylate **7** in 96% yield (Scheme 2). Reaction of the alcohol **7** with γ-methoxyallylstannane **3** in the presence of CSA provided the mixed acetal **8** as a mixture of diastereoisomers in 92% yield.[8] Treatment of **8** with NaCN in DMSO afforded **9** in 92% yield. DIBAL-H reduction of the nitrile **9** followed by Pinnick oxidation of the resulting aldehyde gave carboxylic acid **10**, which was subjected to the Yamaguchi esterification with the alcohol **11** to provide ester **12** in 87% overall yield.[9] Treatment of **12** with TMSI/HMDS gave allylic stannane **13** in 86% yield.[8] Modified Rychnovsky acetylation of the ester **13** provided the α-chloroacetoxy ether **4**.[10,11]



Scheme 2. Reagents and conditions: (a) TsCl, pyridine, 0 ºC, 96%; (b) **7**, CSA, CH_2Cl_2, rt, 92%; (c) NaCN, DMSO, 70 ºC, 92%; (d) (i) DIBAL-H, CH_2Cl_2, -78 ºC; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 0 ºC; (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then **11**, DMAP, toluene, rt, 87% (3 steps); (f) TMSI, HMDS, CH_2Cl_2, -15 to 0 ºC, 86%; (g) DIBAL-H, toluene, -78 ºC, then $(ClCH_2CO)_2O$, DMAP, -78 to 0 ºC.

We next examined the key reaction, intramolecular allylation of **4** (Table 1). In our previous work, the reaction was carried out with $BF_3 \cdot OEt_2$/MS4A in $MeCN/CH_2Cl_2$ to give a 4:1 mixture of the desired products **14** and its diasteroisomer **15** in 60% yield (entry 1).[5] After several experiments, we found that the use of the conditions described in entry 2 gave better result. Thus, the reaction of **4** with $MgBr_2 \cdot OEt_2$/MS5A in toluene provided a 92:8 mixture of **14** and **15** in 85% overall yield. Although actual effects of the conditions used were not clear yet, it contributes to an improvement of the synthesis.

Table 1. The reaction of α-acetoxy ether 4[a]

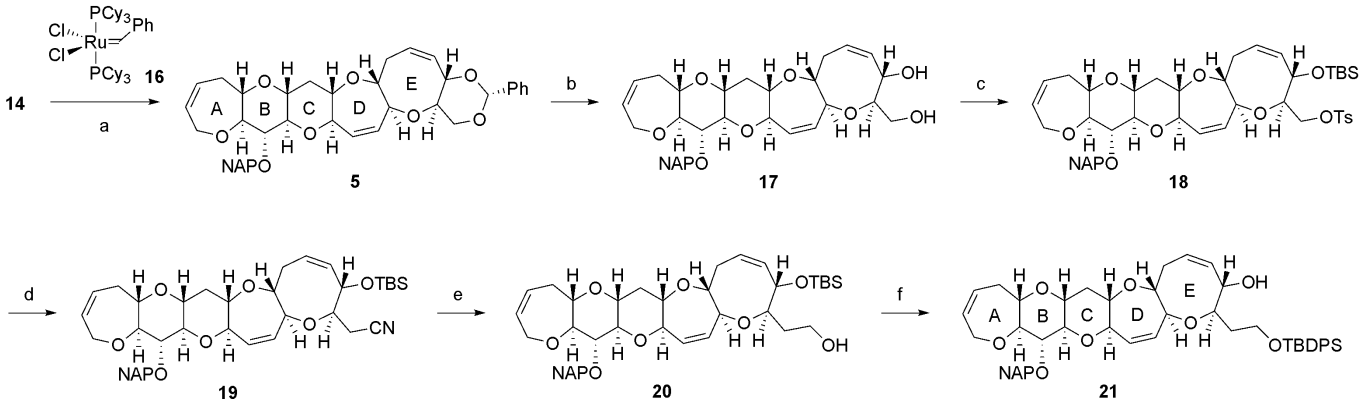


entry	Lewis acid	additive	solvent	temperature	ratio (**14**:**15**)	yield[b]
1	$BF_3 \cdot OEt_2$	MS4A	$MeCN/CH_2Cl_2$ (10:1)	-40 ºC	80 : 20	60%
2	$MgBr_2 \cdot OEt_2$	MS5A	toluene	0 ºC	92 : 8	85%

[a]The reactions were carried out with 5 equiv of Lewis acid. [b]Isolated yields.

Further transformation was carried out as shown in Scheme 3. Ring-closing metathesis of **14** with the Grubbs' catalyst **16** provided the pentacyclic ether **5** in 82% yield (Scheme 3).[12] Thus, the key synthetic intermediate **5** was obtained in 39% overall yield by 10 steps from the diol **6**. In our previous synthesis of **5** from **6**, the overall yield was 11% by 13 steps. Removal of the benzylidene acetal of **5** with CSA in MeOH afforded **17** in 93% yield. Selective tosylation of the primary alcohol of **17** with TsCl/pyridine followed by TBS protection of the remaining secondary alcohol with TBSOTf/2,6-lutidine gave tosylate **18** in 83% overall yield. Treatment of **18** with NaCN in DMSO afforded nitrile **19** in 98% yield. Reduction of **19** with DIBAL-H followed by $LiAlH_4$ provided alcohol **20**. Removal of the TBS protective group of **20** with TBAF followed by selective protection of the remaining primary alcohol with TBDPSCl/Et_3N/DMAP furnished the A-E ring segment **21** in 82% overall yield.

In conclusion, an improved synthesis of the A-E ring segment of ciguatoxin CTX3C (**1**) was performed by using a highly convergent synthetic strategy. Moreover, the key reaction steps, preparation of the *α*-chloroacetoxy ether **3** and its cyclization, were considerably optimized. Further studies towards the total synthesis of **1** are in progress in our laboratory.



Scheme 3. Reagents and conditions: (a) **16**, CH_2Cl_2, reflux, 82%; (b) CSA, MeOH, reflux, 93%; (c) (i) TsCl, pyridine, 0 ºC; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC, 83% (2 steps); (d) NaCN, DMSO, 70 ºC, 98%; (e) (i) DIBAL-H, CH_2Cl_2, -78 ºC; (ii) $LiAlH_4$, THF, -15 to 0 ºC; (f) (i) TBAF, THF, rt; (ii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, reflux, 82% (4 steps).

ACKNOWLEDGEMENTS

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