IMPROVED 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), one of the causative toxin of “ciguatera” seafood poisoning, was isolated from cultured dinoflagellate Gambierdiscus toxicus (Figure 1). The unique structural features and potent neurotoxicity of this molecule have attracted significant attention of synthetic chemists. 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.

Previously, we reported the convergent synthesis of A-E ring segment of 1 as shown in Scheme 1. The ester 2, prepared from an AB ring carboxylic acid and E ring alcohol, was converted to \(\alpha\)-chloroacetoxy ether 4 via the reaction with \(\gamma\)-methoxyallylstannane 3. The intramolecular allylation

Figure 1. Structure of ciguatoxin CTX3C (1)
of 4 followed by ring-closing metathesis provided the A-E ring segment 5. 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 planned to perform the reaction of 3 with the AB ring moiety before the segment coupling. Selective tosylation of known diol 6 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. 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. Treatment of 12 with TMSI/HMDS gave allylic stannane 13 in 86% yield. Modified Rychnovsky acetylation of the ester 13 provided the α-chloroacetoxy ether 4.

Scheme 2. Reagents and conditions: (a) TsCl, pyridine, 0 ºC, 96%; (b) 7, CSA, CH₂Cl₂, rt, 92%; (c) NaCN, DMSO, 70 ºC, 92%; (d) (i) DIBAL-H, CH₂Cl₂, -78 ºC; (ii) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, t-BuOH/H₂O, 0 ºC; (e) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, rt, then 11, DMAP, toluene, rt, 87% (3 steps); (f) TMSI, HMDS, CH₂Cl₂, -15 to 0 ºC, 86%; (g) DIBAL-H, toluene, -78 ºC, then (CICH₂CO)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$_3$·OEt$_2$/MS4A in MeCN/CH$_2$Cl$_2$ to give a 4:1 mixture of the desired products 14 and its diasteroisomer 15 in 60% yield (entry 1). 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$_2$·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

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis acid</th>
<th>additive</th>
<th>solvent</th>
<th>temperature</th>
<th>ratio (14:15)</th>
<th>yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$·OEt$_2$</td>
<td>MS4A</td>
<td>MeCN/CH$_2$Cl$_2$ (10:1)</td>
<td>-40 °C</td>
<td>80 : 20</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>MgBr$_2$·OEt$_2$</td>
<td>MS5A</td>
<td>toluene</td>
<td>0 °C</td>
<td>92 : 8</td>
<td>85%</td>
</tr>
</tbody>
</table>

$^a$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). 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 TBDPSCI/Et$_3$N/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, CH₂Cl₂, reflux, 82%; (b) CSA, MeOH, reflux, 93%; (c) (i) TsCl, pyridine, 0 ºC; (ii) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 ºC, 83% (2 steps); (d) NaCN, DMSO, 70 ºC, 98%; (e) (i) DIBAL-H, CH₂Cl₂, -78 ºC; (ii) LiAlH₄, THF, -15 to 0 ºC; (f) (i) TBAF, THF, rt; (ii) TBDPSCI, Et₃N, DMAP, CH₂Cl₂, reflux, 82% (4 steps).

ACKNOWLEDGEMENTS
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REFERENCES AND NOTES
6. For the synthesis of the A-E ring segment of 1 by other groups, see: (a) M. Maruyama, K. Maeda, T. Oishi, H. Oguri, and M. Hirama, Heterocycles, 2001, 54, 93; (b) M. Maruyama, M. Inoue, T. Oishi,


