Highly Stereocontrolled Synthesis of the ABCD Ring Fragment of Ciguatoxin CTX3C

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This paper is dedicated to Professor Ryoji Noyori for his outstanding achievements in synthetic organic chemistry.

Abstract: A combination of asymmetric alkylation using (1R,2S)-1-amino-2-indanol derivative as a chiral auxiliary and the ring-closing metathesis reaction was shown to be an efficient method for synthesizing the ABCD ring fragment of ciguatoxin CTX3C.

Key words: ciguatoxin CTX3C, polycyclic ether, asymmetric alkylation, ring-closing metathesis, multiple asymmetric induction

Ciguatoxin CTX3C (1) is one of the causative toxins of ciguatera seafood poisoning prevalent in the tropics and subtropics. During the course of our synthetic studies directed toward ciguatoxins, we developed a highly convergent strategy for synthesizing polycyclic ethers based on a combination of alkylation and ring-closing metathesis (RCM) reactions, and have recently succeeded in synthesizing the ABCDE ring fragments of ciguatoxins. However, stereoselectivity of the alkylation step in the synthesis of the ABCDE fragment of 1 was low and the unnatural type diastereomer even predominated. Therefore, it became necessary to epimerize the epimer at a specific stage, lengthening the synthesis procedure that had only a moderate overall yield. In this paper, we describe the efficient synthesis of the ABCD ring fragment (2) of 1 through highly stereoselective alkylation and RCM reactions.

Transformation of 7 to the ABCD ring fragment 2 is shown in Scheme 2. Selective removal of the p-methoxybenzylidene acetal of 7 using pyridinium p-toluenesulfonate (PPTS) in 1-propanol and the subsequent protection of the resulting 1,3-diol as bis-t-butyldiphenylsilyl (bis-TBPS) ether afforded 8 in 75% yield (2 steps). Removal of the MPM group of 10 gave alcohol 11, which was treated with camphorsulfonic acid (CSA) in toluene at 80 °C to yield lactone 12 (60%). Although addition of
vinylmagnesium bromide resulted in a low yield of 13, vinylolithium generated from tributy(vinyl)tin and methylolithium reacted with 12 and gave 13 in 98% yield. Conversion of the hemiacetal 13 to the methacetal 14 as a mixture of diastereomers in a 2:1 ratio and the subsequent reduction with triethylsilane in the presence of a mixture of diastereomers in a 2:1 ratio and the subsequent reduction with triethylsilane in the presence of $BF_3\cdot OEt_2$ gave 15. The RCM reaction of the diene 15 using Grubbs catalyst (7) was too sluggish, presumably due to steric hinderance of the TBPS groups. The bis-TBPS ether 15 was then converted to the less hindered diacetate 16 in two steps (85%). The RCM reaction of 16 proceeded smoothly to afford the ABCD ring fragment 2 of 1 in 74% yield. The stereochemistry of 2 was unambiguously determined by NOE experiments (Scheme 2).

In conclusion, a highly convergent, efficient and stereoselective synthesis of the ABCD ring fragment 2 of CTX3C (1) was achieved. The present asymmetric alkylation and ring-closing metathesis sequence will serve as a powerful tool for the synthesis of polycyclic ether toxins.

### References and Notes

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Table 1: Alkylation of 4 and 5 with Iodide 3

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>4 or 5 (eq)</th>
<th>yield/%</th>
<th>6(7):8(9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>THF-HMPA</td>
<td>4(2)</td>
<td>23</td>
<td>1:2</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>THF-DMPU</td>
<td>4(2)</td>
<td>43</td>
<td>1:10</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>THF</td>
<td>5(4)</td>
<td>26</td>
<td>2:1</td>
</tr>
<tr>
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<td>BuLi</td>
<td>THF</td>
<td>5(4)</td>
<td>25</td>
<td>10:1</td>
</tr>
<tr>
<td>5</td>
<td>BuLi</td>
<td>THF-HMPA</td>
<td>5(4)</td>
<td>26</td>
<td>10:1</td>
</tr>
<tr>
<td>6</td>
<td>BuLi</td>
<td>THF-DMPU</td>
<td>5(4)</td>
<td>96</td>
<td>10:1</td>
</tr>
<tr>
<td>7</td>
<td>BuLi</td>
<td>THF-DMPU</td>
<td>5(2)</td>
<td>73</td>
<td>10:1</td>
</tr>
<tr>
<td>8</td>
<td>BuLi</td>
<td>THF-DMPU</td>
<td>5(1)</td>
<td>26</td>
<td>10:1</td>
</tr>
</tbody>
</table>

*Carried out at -78 °C to rt.

One equivalent of base was added to 4 or 5.

The ratio of THF-HMPA or THF-DMPU is 10:1 (v/v).

Based on iodide 3.

Determined by 500 MHz ¹H NMR.

### Scheme 2

Reagents and conditions. (a) PPTS, 1-propanol, rt, 5 h, 82%; (b) TBPSCl, imidazole, DMF, 60 °C, 6 h, 92%; (c) DDQ, CH₂Cl₂, H₂O, rt, 1 h, 75%; (d) CSA, toluene, 80 °C, 1 d, 60%; (e) tributyl(vinyl)tin, MeLi, THF, -78 °C, 30 min. 98%; (f) HC(OMe)₃, p-TsOH, THF, -30 °C, 2 h, 61%; (g) TBAF, THF, rt, 4 h; (i) Ac₂O, Py, DMAP, rt, 4 h, 85% (2 steps); (j) 17, CH₂Cl₂, reflux, 12 h, 74%.


(9) r-Butyllithium is also usable and gave a very similar result.


(13) Physical data of 2: [α]D 30  = -6.33 (c 0.42, CHCl3); IR (film) ν 3027, 2932, 1744, 1453, 1369, 1241, 1107, 753, 697 cm-1; 1H NMR (500 MHz, CDCl3) δ 1.61 (1H, q, J = 11.5 Hz, H10ax), 2.87 (3H, s, Ac), 2.89-2.89 (2H, m, H8, H9), 3.27 (1H, td, J = 12.0, 6.0 Hz, H1), 3.34 (1H, t, J = 9.5 Hz, H6), 3.36 (1H, dd, J = 11.5, 9.5, 5.0 Hz, H11), 3.47 (1H, t, J = 9.5 Hz, H7), 3.79 (1H, dd, J = 9.5, 6.0, 2.5 Hz, H16), 3.94 (1H, dd, J = 9.5, 2.0 Hz, H12), 4.01 (1H, d, J = 15.0, 3.0 Hz, H1), 4.04 (1H, dd, J = 12.0, 2.5 Hz, H17), 4.09 (1H, dd, J = 12.0, 6.0 Hz, H17), 4.29 (1H, dd, J = 15.0, 6.0 Hz, H11), 4.83 (1H, d, J = 12.0 Hz, OCHPh), 4.88 (1H, d, J = 12.0 Hz, OCHPh), 5.44 (1H, d, J = 9.5, 2.0 Hz, H15), 5.52 (1H, dt, J = 11.5, 2.0 Hz, H14), 5.74 (1H, dd, J = 11.5, 2.0 Hz, H13), 5.77 (1H, ddt, J = 12.0, 8.0, 3.0 Hz, H3), 5.86 (1H, ddt, J = 12.0, 6.0, 3.0 Hz, H2), 7.24-7.29 (1H, m), 7.33 (2H, t, J = 7.5 Hz), 7.39 (2H, d, J = 7.5 Hz); 13C NMR (125 MHz, CDCl3) δ 20.82, 20.96, 34.59, 36.60, 46.36, 64.25, 65.4, 74.81, 75.09, 75.15, 76.87, 79.06, 80.05, 80.41, 80.95, 82.06, 87.33, 126.65, 127.43, 127.71, 128.19, 129.71, 131.33, 132.39, 134.82, 139.12, 143.72, 149.67, 154.69, 154.84, 161.1, 161.2, 169.60, 170.72; MALDI-TOF MS calcd for C32H36O9 (M+Na) 537.21, found 537.13.

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