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Synthesis of the LMN-ring fragment of the Caribbean ciguatoxin C-CTX-1

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Abstract—Ciguatoxin C-CTX-1 was isolated as a principal causative toxin of ciguatera seafood poisoning in the Caribbean Sea, and is structurally classified as a ladder-shaped polycyclic ether. In this Letter, we report the synthesis of the tricyclic LMN-ring system of C-CTX-1. SmI_2-mediated reductive cyclization efficiently constructed the seven-membered M-ring with the axially oriented 1,3-dimethyl structure.
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Ciguatoxins, the principal causative toxins of ciguatera seafood poisoning, are large ladder-like polycyclic ethers.[1] To date, more than 20 ciguatoxin congeners have been structurally identified.[2] Ciguatera causes diverse and often long-lasting human health problems. The severity, number and duration of ciguatera symptoms reflect a combined influence of dose, toxin profile and individual susceptibility. In the Pacific Ocean, neurological symptoms predominate, while in the Caribbean Sea, gastrointestinal symptoms are a dominant feature of the disease.[1b] These quantitative differences in symptoms could originate from the structural differences between Pacific and Caribbean ciguatoxins; in contrast to 13 ether rings in the Pacific ciguatoxins, Caribbean ciguatoxin C-CTX-1 (**1**, Fig. 1)[3] possesses 14 ether rings with distinct functional group patterns.

The very limited supply of ciguatoxins from natural sources has prevented structure–symptom relationship studies as well as development of therapeutic methods for ciguatera. To address these issues, we recently synthesized three Pacific ciguatoxins[4,5] and developed immunochemical methods for their detection.[6] Here, we report the synthesis of LMN-ring moiety **4** of Caribbean ciguatoxin **1**, which could be useful both for preparing anti-ciguatoxin antibodies and as a fragment for its total synthesis.

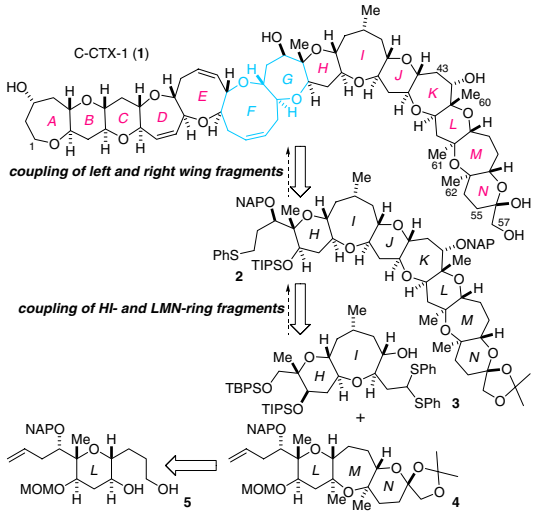

Figure 1. Structures of the Caribbean ciguatoxin C-CTX-1 and retrosynthesis of the right wing fragment of C-CTX-1.

Tricyclic fragment **4** (Fig. 1) was designed to be coupled with HI-ring **3** to generate the right wing fragment **2**, which would be further assembled with the previously reported ABCDE-ring fragment[7] to deliver C-CTX-1 **1**. The convergent strategies necessary for these two couplings were recently developed and applied to the total

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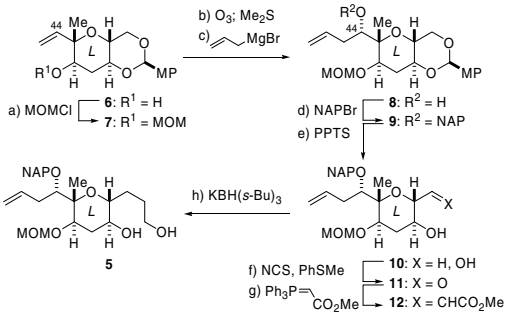
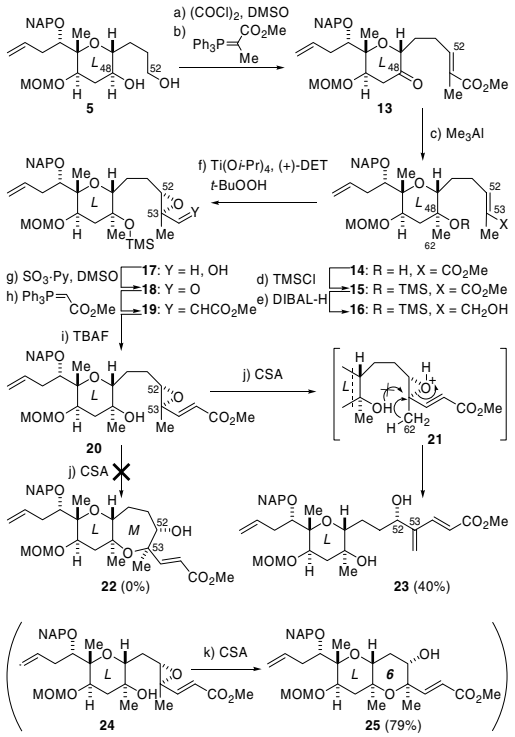
synthesis of the Pacific ciguatoxins.[4,8] LMN-ring portion **4** is the most heavily substituted sub-structure of **1**; three of the four angular methyl groups are present in this region. In particular, the M-ring posed a significant synthetic challenge, because the two sterically demanding methyl groups are placed in a 1,3-diaxial relationship on the strained seven-membered ring.[9] Although a number of strategies for the construction of oxepane rings have been developed,[10] no general method was available for building the bis-trisubstituted alkyl ether in the oxepane format. Therefore, we planned a flexible synthetic strategy so that various methodologies could be applied to the M-ring cyclization, starting from the common L-ring fragment **5**. After synthesis of the LM-ring system, the N-ring would be constructed to furnish **4**.

First, the two side chains of the six-membered ring **6**[11] were modified (Scheme 1). MOM-protection of alcohol **6**, ozonolysis of the terminal olefin of **7**, and subsequent allylation with a Grignard reagent in THF[12] gave secondary alcohol **8** as the major stereoisomer (2.1:1). Introduction of the 2-naphthylmethyl (NAP)[13] group to alcohol **8**, followed by removal of the *p*-methoxyphenyl (MP) acetal from **9**, produced 1,3-diol **10**. Chemoselective oxidation of the primary alcohol of diol **10** was realized by using the modified Corey–Kim oxidation,[14] leading to aldehyde **11**. Then, compound **11** was exposed to a Wittig reagent to give the α,β-unsaturated olefin **12**, reduction of which with KBH(*s*-Bu)$_3$ resulted in the saturated 1,5-diol **5**.[15]

Our first strategy for synthesizing the seven-membered M-ring was based on the acid-catalyzed, 7-*endo* selective, cyclization of hydroxy epoxides, developed by Nicolaou (Scheme 2).[16] Before the cyclization, the appropriate functional groups were introduced into **5**. Swern oxidation of diol **5** generated the dicarbonyl compound, the aldehyde group of which was reacted with a Wittig reagent to produce α-methyl-α,β-unsaturated ester **13**. Axial-attack of Me_3Al on the C48-ketone of **13** led to tertiary alcohol **14** as the sole isomer.[17] After



Scheme 1. Reagents and conditions: (a) MOMCl, *i*-Pr$_2$NEt, 1,2-dichloroethane, reflux, 99%; (b) O_3, pyridine/CH_2Cl_2/MeOH (1:3:4), −78 °C, then Me_2S; (c) CH_2=$CHCH_2MgBr$, THF, −100 °C, 59% (**8**), 28% (C44-epimer) (two steps); (d) NAPBr, TBAI, NaH, THF/DMF (3:1), rt; (e) PPTS, MeOH, 94% (two steps); (f) NCS, PhSMe, CH_2Cl_2, −20 °C, then *i*-Pr$_2$NEt, −78 °C; (g) Ph_3P=$CHCO_2Me$, THF, rt, 62% (*E*/*Z* = 1:2, two steps); (h) KBH(*s*-Bu)$_3$, *t*-BuOH, THF, −100 to 0 °C, 85%.



Scheme 2. Reagents and conditions: (a) (COCl)$_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (b) Ph_3P=C(Me)CO_2Me, toluene, rt, 56% (two steps); (c) Me_3Al, CH_2Cl_2, −78 °C to −15 °C, 81%; (d) TMSCl, imidazole, CH_2Cl_2, rt; (e) DIBAL-H, CH_2Cl_2, −78 °C, 89% (two steps); (f) Ti(O*i*-Pr)$_4$, (+)-diethyl L-tartrate, *t*-BuOOH, 4 Å MS, CH_2Cl_2, 89%; (g) SO_3·Py, Et_3N, DMSO, CH_2Cl_2, rt; (h) Ph_3P=$CHCO_2Me$, toluene, rt; (i) TBAF, THF, 72% (three steps); (j) CSA, CH_2Cl_2, 0 °C to rt, 0% (**22**), 40% (**23**); (k) CSA, CH_2Cl_2, 0 °C, 79%.

conversion of alcohol **14** to its TMS ether, the ester of **15** was reduced with DIBAL-H to generate **16**. Sharpless asymmetric epoxidation[18] of allylic alcohol **16** led stereoselectively to epoxide **17**. Following the Nicolaou method, a π-bond was placed adjacent to the epoxide unit in order to facilitate the 7-*endo* cyclization through cleavage of the C53–O bond. Thus, SO_3·pyridine oxidation of **17** and subsequent Wittig olefination of **18** produced **19**, the TMS group of which was removed to give hydroxy epoxide **20**. However, to our disappointment, a variety of acid catalysts failed to transform **20** into oxepane **22**. Instead, diene **23** was generated under these conditions in 40% yield via C62-proton elimination/epoxide opening (see **21**). Interestingly, the lower homologue **24** was successfully converted to tetrahydropyran **25** in 79% yield under the same conditions.[19] These two contrasting results reflect the significant difference in cyclization efficiency between the six- and seven-membered rings. A more powerful method was clearly required to construct the dimethyl-substituted M-ring.

As shown in Scheme 3, we next adopted Nakata's SmI_2-induced reductive intramolecular cyclization[20,21] to construct the M-ring. Cyclization substrate **31** was prepared in seven steps from the common intermediate **5**. The primary alcohol of diol **5** was selectively masked with a TBS

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