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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.

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.

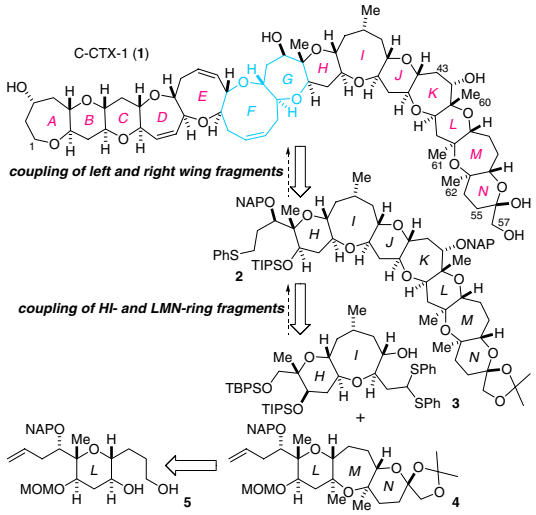

Figure 1. Structures of the Caribbean ciguatoxin C-CTX-1 and retrosynthesis of the right wing fragment of C-CTX-1.

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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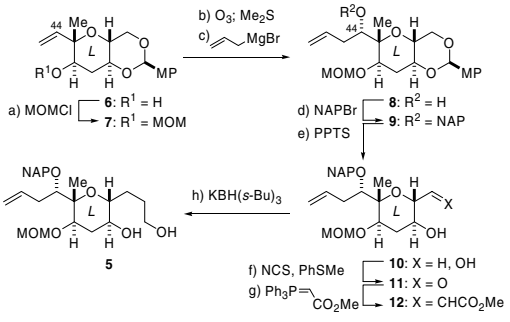
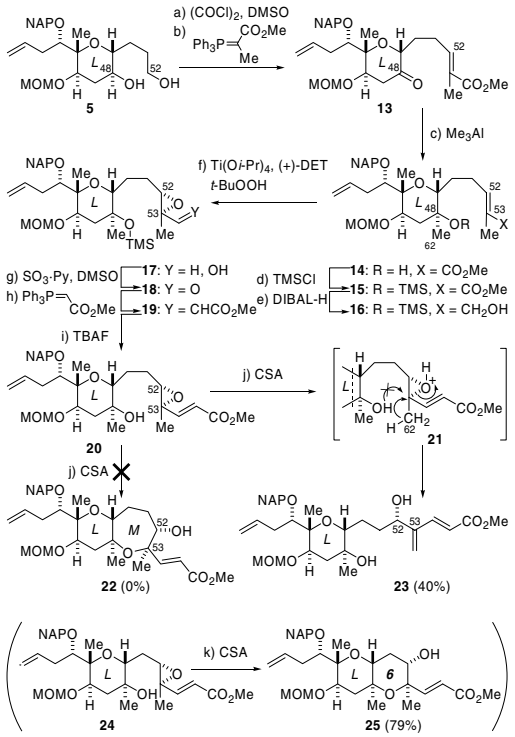
synthesis of the Pacific ciguatoxins.[4,8] LMN-ring portion **4** is the most heavily substituted sub-structure of **1**; three of the four angular methyl groups are present in this region. In particular, the M-ring posed a significant synthetic challenge, because the two sterically demanding methyl 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



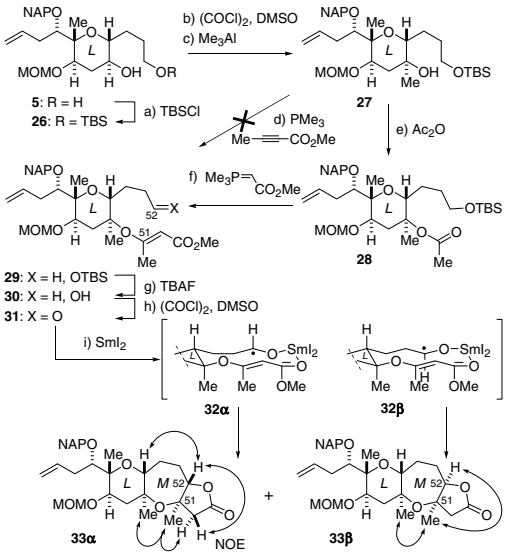
Scheme 1. Reagents and conditions: (a) MOMCl, *i*-Pr$_2$NEt, 1,2-dichloroethane, reflux, 99%; (b) O_3, pyridine/CH_2Cl_2/MeOH (1:3:4), −78 °C, then Me_2S; (c) CH_2=$CHCH_2MgBr$, THF, −100 °C, 59% (**8**), 28% (C44-epimer) (two steps); (d) NAPBr, TBAI, NaH, THF/DMF (3:1), rt; (e) PPTS, MeOH, 94% (two 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

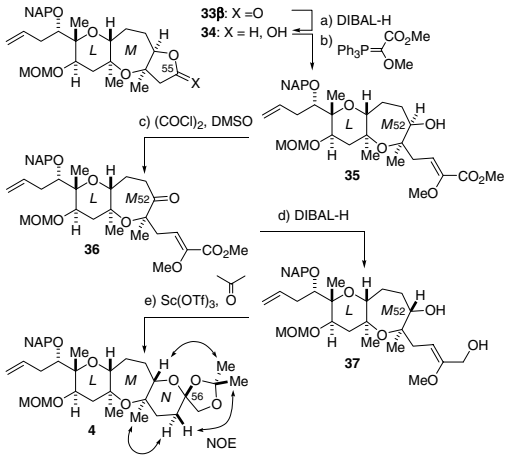


Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 0 °C, 99%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 89%; (c) Me_3Al, CH_2Cl_2, −90 °C to −30 °C, 87%; (d) $MeC{\equiv}CCO_2Me$, Me_3P, CH_2Cl_2, rt to reflux, 0%; (e) Ac_2O, DMAP, CH_2Cl_2, rt, 90%; (f) $Me_3P{=}CHCO_2Me$, toluene, 200 °C, 33% (57% of **28** was recovered); (g) TBAF, THF, rt; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, 99% (two steps); (i) SmI_2, THF (1 mM), rt, 24 h, 42% (**33α**:**33β** = 1:3, based on 85% conversion), 44% (**30**, based on 85% conversion).

group to generate **26**. Swern oxidation of the remaining secondary alcohol of **26**, followed by stereoselective methylation, resulted in **27**. However, PMe_3-induced hetero Michael-addition[22] of tertiary alcohol **27** to the corresponding tetrolic acid methyl ester did not proceed, presumably due to the bulky nature of the nucleophile. We thus developed a new two-step protocol to produce β-alkoxy crotonate **29**. Acetylation of **27** led to ester **28**, olefination of which was realized using highly reactive methyl (trimethylphosphoranylidene)acetate to afford enol ether **29**.[23] Noteworthily, the tributyl- and triphenylphosphoranylidene derivatives[24] did not induce this 'non-classical' Wittig olefination of ester **28**.

Removal of the TBS group from **29**, followed by Swern oxidation, gave aldehyde **31**. Gratifyingly, SmI_2-promoted 7-*exo* radical cyclization in THF under dilute conditions (1 mM) transformed **31** into the seven-membered M-ring (42% yield, **33α**:**33β** = 1:3). Cyclization products **33α** and **33β** were determined to be C52-epimers with the desired C51-stereochemistry. Radical intermediates **32α** and **32β**, conformationally fixed by chelation of Sm(III), most likely lead to **33α** and **33β**, respectively, through C–C bond formation and subsequent lactonization.

Construction of the N-ring to the major isomer **33β** gave rise to the desired LMN-ring fragment **4** (Scheme 4). DIBAL-H-reduction of lactone **33β** to the corresponding lactol **34**, followed by Wittig olefination,[25] afforded α-methoxy-α,β-unsaturated ester **35**. Alcohol **35** was oxidized under Swern conditions to generate ketone **36**, which was treated with DIBAL-H, leading to diol **37** as the major isomer. In this reaction, the β-selective



Scheme 4. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −90 °C; (b) $Ph_3P{=}C(OMe)CO_2Me$, toluene, 110 °C, 52% (two steps); (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 89%; (d) DIBAL-H, CH_2Cl_2, −100 °C, 61% (**37**), 11% (C52-epimer); (e) $Sc(OTf)_3$, acetone, 83%.

attack of hydride on the ketone of **36** set the desired C52-stereochemistry. Lastly, construction of the acetonide-protected N-ring from methyl enol ether **37** was achieved by direct acetalization in acetone in the presence of $Sc(OTf)_3$.[26] Under these conditions, the thermodynamically more stable C56-spiroacetal **4** was formed as the sole stereoisomer.[27]

In summary, the synthesis of the LMN-ring fragment of the Caribbean ciguatoxin C-CTX-1 was established in a stereoselective manner. Key reactions of the synthesis include (i) an acetylation/Wittig reaction sequence to introduce the branched enol ether structure (**27**→**29**); (ii) the SmI_2-mediated reductive cyclization to construct the seven-membered M-ring with the axially oriented 1,3-dimethyl structure (**31**→**33**); (iii) a $Sc(OTf)_3$-promoted acetalization to build the acetonide-protected N-ring (**37**→**4**). Synthesis of the right wing fragment of C-CTX-1 from **4** is currently underway, and will be reported in due course.

Acknowledgements

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27. *Physical data for* **4**: $[\alpha]_D^{26}$ −47.31 (*c* 1.00, $CHCl_3$); IR (film) 2951, 1639, 1464, 1379, 1209, 1105, 1039, 984, 913, 865, 816, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, s, Me63), 1.28 (3H, s, Me60), 1.31 (3H, s, Me61), 1.40 (3H, s, Me), 1.51 (3H, s, Me), 1.65–1.70 (4H, m, H47, 50, 55 × 2), 1.72–1.79 (3H, m, H51 × 2, 54), 1.86–1.93 (2H, m, H50, 54), 2.06 (1H, dd, $J = 12.0$, 5.0 Hz, H47), 2.41 (1H, ddd, $J = 15.5$, 6.5, 4.0 Hz, H43), 2.45 (1H, ddd, $J = 15.5$, 9.0, 7.0 Hz, H43), 3.33 (3H, s, MOM), 3.49 (1H, dd, $J = 9.0$, 4.0 Hz, H44), 3.66 (1H, dd, $J = 11.0$, 5.0 Hz, H49), 3.69 (1H, d, $J = 8.5$ Hz, H57), 3.88 (1H, dd, $J = 12.0$, 5.0 Hz, H46), 3.88 (1H, d, $J = 9.0$ Hz, H52), 3.93 (1H, d, $J = 8.5$ Hz, H57), 4.58 (1H, d, $J = 7.0$ Hz, MOM), 4.62 (1H, d, $J = 7.0$ Hz, MOM), 4.76 (1H, d, $J = 12.0$ Hz, NAP), 4.86 (1H, d, $J = 12.0$ Hz, NAP), 5.01 (1H, dd, $J = 10.0$, 2.0 Hz, H41), 5.11 (1H, dd, $J = 17.0$, 2.0 Hz, H41), 5.93 (1H, dddd, $J = 17.0$, 10.0, 7.0, 6.5 Hz, H42), 7.43–7.49 (3H, m, NAP), 7.77–7.82 (4H, m, NAP); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 18.8, 20.4, 24.7, 25.2, 26.9, 27.4, 30.5, 35.2, 37.2, 42.8, 56.0, 72.9, 73.0, 73.8, 74.4, 74.7, 76.2, 77.9, 79.8, 84.6, 95.8, 103.2, 111.2, 116.2, 125.8, 126.0, 126.4, 126.5, 127.8, 127.9, 128.0, 133.0, 133.4, 136.8, 137.4; HRMS (ESI), Anal. Calcd for $C_{36}H_{50}NaO_8$ $(M+Na)^+$ 633.3403, found 633.3401.