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Convergent Synthesis of the HIJKLM Ring System of Ciguatoxin CTX3C

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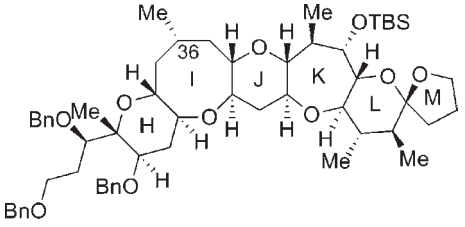
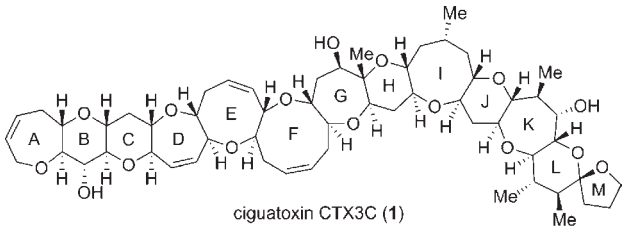
ABSTRACT



The HIJKLM ring system of ciguatoxin CTX3C was synthesized in a convergent manner. The key steps were a conjugate addition/alkylation sequence, spiroacetalization, intramolecular allylation, ring-closing metathesis, and hydrogenation to form the 36-α-methyl substituent.

Ciguatera is a principal source of food poisoning caused in tropical and subtropical areas.[1,2] According to recent research, overall, the global number of poisonings is estimated to be 50 000−500 000 cases annually. Ciguatoxin CTX3C



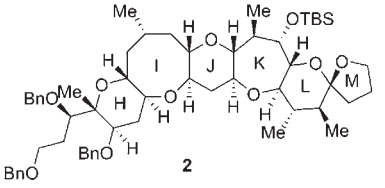


Figure 1. Structures of ciguatoxin CTX3C (**1**) and the HIJKLM ring system **2**.

(**1**, Figure 1)[3] was isolated from cultured dinoflagellate *Gambierdiscus toxicus* by Yasumoto and co-workers and was found to be one of the causative toxins of ciguatera seafood poisoning. This molecule exhibits potent neurotoxicity [LD_{50} (mouse, ip): 1.3 μg/kg] by binding to the voltage-sensitive sodium channels. Its structural complexity, strong biological activity, and limited availability from natural sources have attracted much attention from the synthetic community.[4,5]

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(4) For total synthesis of ciguatoxin CTX3C (**1**), see: (a) Hirama, M; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904. (b) Inoue, M.; Uehara, H.; Maruyama, M.; Hirama, M. *Org. Lett.* **2002**, *4*, 4551. (c) Inoue, M.; Miyazaki, K.; Uehara, H.; Maruyama, M.; Hirama, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12013. (d) Inoue, M.; Hirama, M. *Synlett* **2004**, 577. (e) Inoue, M.; Hirama, M. *Acc. Chem. Res.* **2004**, *37*, 961. (f) Hirama, M. *Chem. Rec.* **2005**, *5*, 240. (g) Yamashita, S.; Ishihara, Y.; Morita, H.; Uchiyama, J.; Takeuchi, K.; Inoue, M.; Hirama, M. *J. Nat. Prod.* **2011**, *74*, 357.

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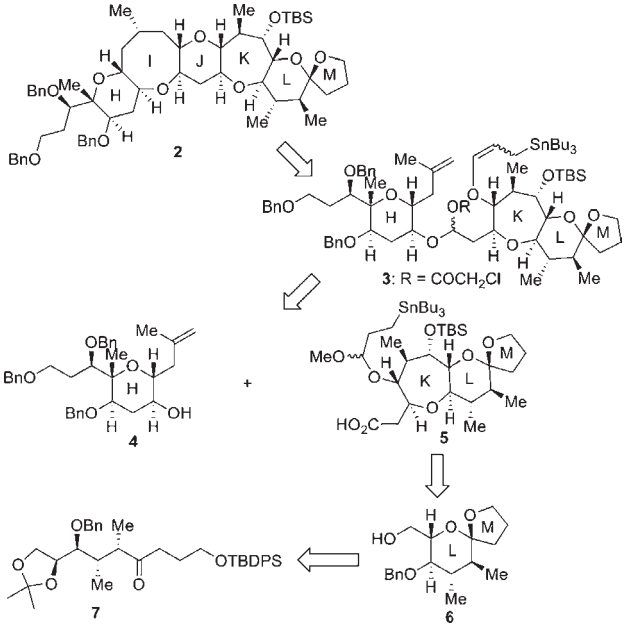
Herein, as a part of our efforts toward the total synthesis of **1**,[6] we describe a convergent synthesis of the HIJKLM ring system **2** (Figure 1).

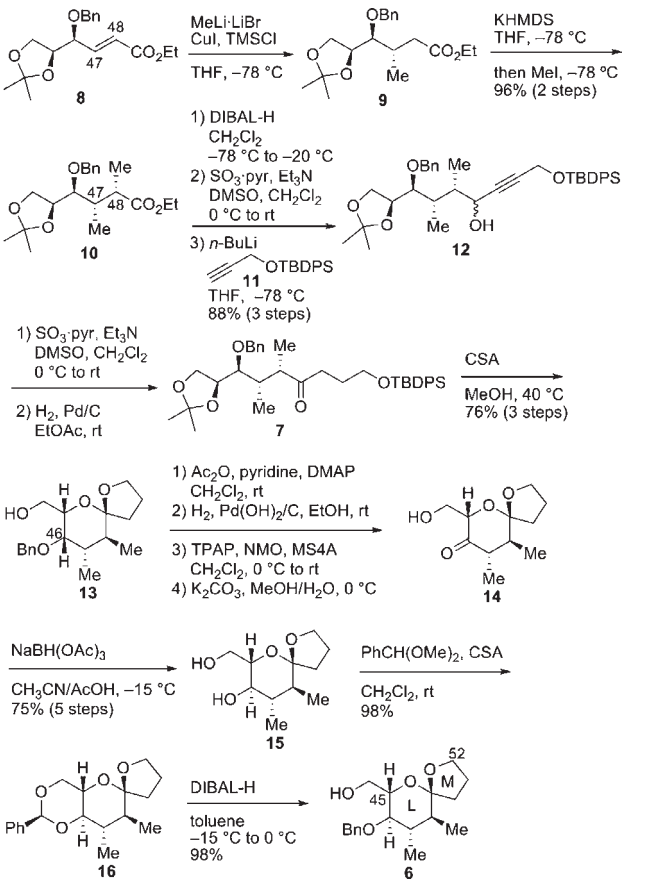
Our retrosynthetic analysis of **2** is outlined in Scheme 1. We envisaged that the IJ ring moiety of **2** could be constructed via intramolecular allylation and subsequent ring-closing metathesis of allylic stannane **3**.[7] The cyclization precursor **3** was broken down into two coupling precursors, alcohol **4** and carboxylic acid **5**. The KLM ring system **5** could be synthesized from the LM ring system **6**, of which the carbon framework could be constructed via spiroacetalization of linear compound **7**.

Scheme 1. Retrosynthetic Analysis of **2**



The synthesis of the LM ring system **6** commenced from known α,β-unsaturated ester **8** (Scheme 2).[8] Stereoselective introduction of the vicinal dimethyl groups at the C47 and C48 positions[9] was performed by the sequential 1,2-chiral induction according to Hanessian's protocol.[10] Thus, treatment of the acyclic compound **8** with MeLi•LiBr/CuI/TMSCl gave conjugate addition product **9**. The potassium enolate, derived from **9** with KHMDS, reacted with MeI to provide methylated adduct **10**[11] in 96% yield for two steps as a single stereoisomer, as judged by its 400 MHz ^{1}H NMR spectrum. Reduction of the ester

Scheme 2. Synthesis of **6**



10 with DIBAL-H and subsequent Parikh–Doering oxidation[12] of the resulting alcohol afforded the corresponding aldehyde. Reaction of the aldehyde with the lithium acetylide, prepared from alkyne **11**,[13] proceeded to give alcohol **12** as a 1:1 diastereomeric mixture. Oxidation of the alcohol **12** followed by hydrogenation of the alkyne moiety yielded the linear compound **7**. Removal of the acetonide and TBDPS protective groups and spiroacetalization were performed with CSA in MeOH to provide the thermodynamically stable spiroacetal **13** as the sole product in 76% yield for three steps.[14,15] Next, we investigated the stereochemical inversion of the C46 position. The alcohol **13** was transformed to hydroxy ketone **14** by the four step sequence: (1) acetylation, (2) debenzylation, (3) TPAP oxidation,[16] and (4) deacetylation. Diastereoselective reduction of **14** with $NaBH(OAc)_3$[17] proceeded

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(8) Ermolenko, L.; Sasaki, N. A. *J. Org. Chem.* **2006**, *71*, 693.

(9) The carbon numbering corresponds to that of the natural product.

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(15) The structural determination of the resulting spiroacetal chiral center was performed at the stage of compound **6**.

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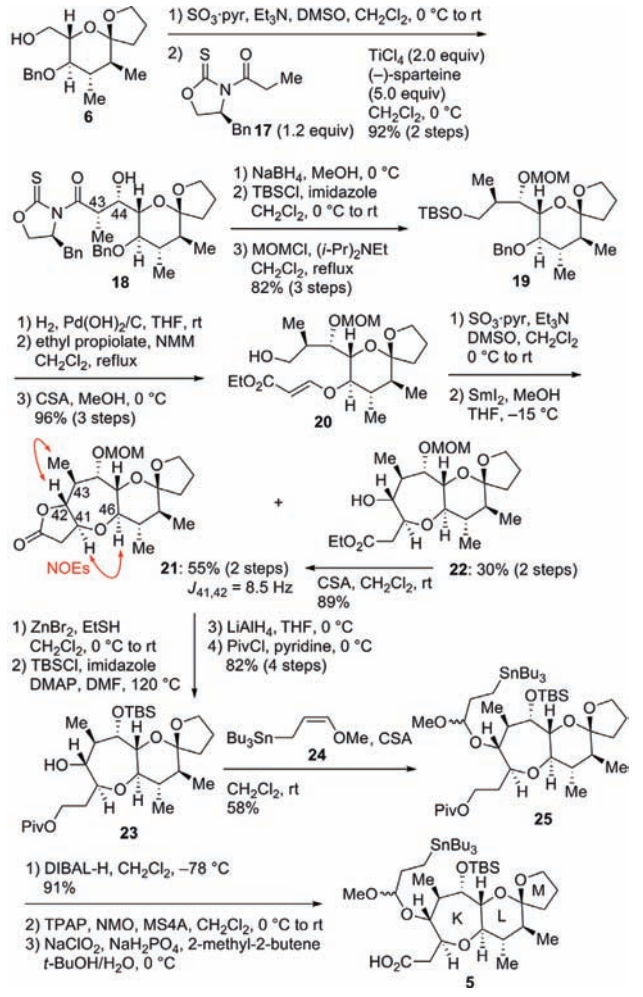
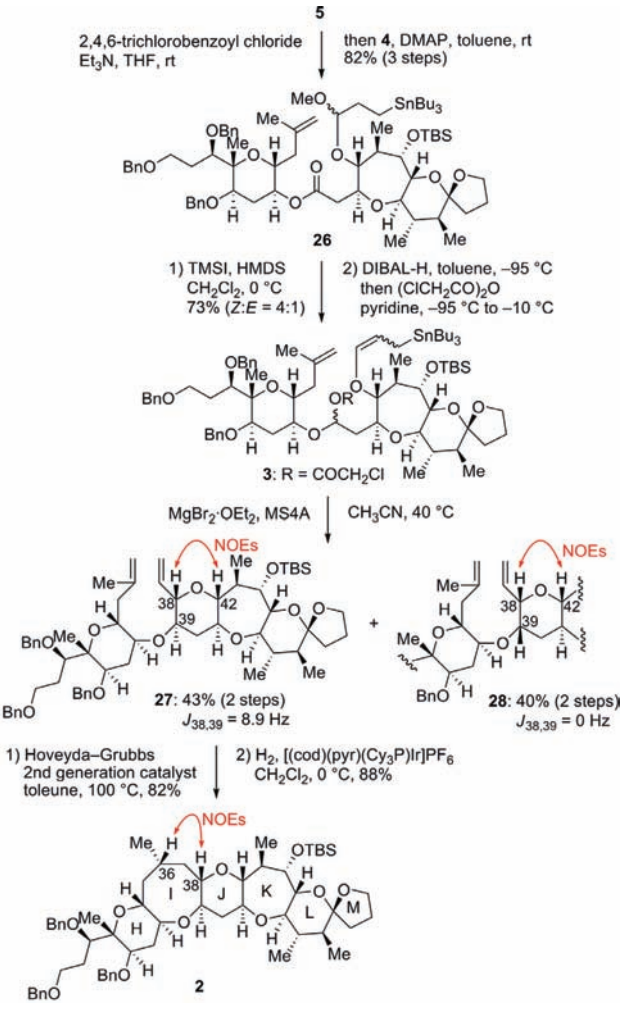
(17) Saksena, A.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273.

Scheme 3. Synthesis of **5**



Scheme 4. Synthesis of **2**



smoothly to afford diol **15** as a single stereoisomer. Protection of **15** with $PhCH(OMe)_2$ provided benzylidene acetal **16**, and subsequent acetal cleavage of **16** with DIBAL-H gave the LM ring system **6**. The observed NOE between H-45 and H_2-52 of **6** confirmed the stereochemistry of the spiroacetal moiety which had emerged from the conversion of **7** to **13**.

The transformation of **6** to the KLM ring system **5** is described in Scheme 3. The aldol reaction of the aldehyde, prepared from alcohol **6**, with propionyl oxazolidinethione **17** (1.2 equiv) was performed in the presence of $TiCl_4$ (2.0 equiv)/(−)-sparteine (5.0 equiv) to give the *syn* aldol adduct **18** as a single stereoisomer in 92% yield in two steps.[18] The absolute configuration at the C44 position was determined by the modified Mosher method.[19] The structural determination at the C43 position was carried out at a later stage. The oxazolidinethione chiral auxiliary was removed with $NaBH_4$, and the primary and secondary hydroxy groups were protected with TBSCl and MOMCl, respectively, to afford MOM ether **19** in 82% yield in three steps. After deprotection of the benzyl group of **19** by hydrogenolysis, the resulting alcohol was reacted with ethyl propiolate in the presence of NMM to yield the corresponding α,β-unsaturated ester. The TBS moiety was deprotected with CSA in MeOH to give alcohol **20**. The alcohol **20** was oxidized to the aldehyde with SO_3•pyr/Et_3N/DMSO,[12] and the aldehyde was treated with SmI_2 in the presence of MeOH[20] to afford lactone **21** and hydroxy ester **22** in 85% combined yield in two steps. The hydroxy ester **22** was converted to **21** with CSA. The NOEs of H-41/H-46 and H-42/Me-43 of **21** confirmed that they were in a *syn* relationship to each other. The large magnitude of $J_{41,42}$ (8.5 Hz) indicated that H-41 and H-42 were in an axial−axial relationship. Removal of MOM group with

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$ZnBr_2$/EtSH[21] and silylation of the resulting hydroxy moiety gave the corresponding TBS ether. Reduction of the lactone moiety with $LiAlH_4$ followed by selective protection of the primary hydroxy group with PivCl provided pivalate **23**. Acid-catalyzed acetal formation of **23** with γ-methoxyallylstannane **24** afforded mixed acetal **25**.[22] Deprotection of the pivaloyl moiety followed by stepwise oxidation with TPAP[16] and $NaClO_2$[23] gave the carboxylic acid **5**.

The KLM ring fragment **5** was connected to the H ring fragment **4**[24] under Yamaguchi conditions[25] to provide ester **26** in 82% yield in three steps (Scheme 4). Treatment of **26** with TMSI/HMDS[22] gave the allylic stannane as a 4:1 *Z*/*E* diastereomeric mixture in 73% yield. Reduction of the ester moiety with DIBAL-H followed by trapping of the resulting aluminum hemiacetal with $(ClCH_2CO)_2O$/pyridine[26,27] afforded the α-chloroacetoxy ether **3**.[28] Intramolecular allylation of **3** was carried out with $MgBr_2 \bullet OEt_2$/MS4A in CH_3CN at 40 °C to give the desired product **27** and its 39-epimer **28** in 43% and 40%, respectively, in two steps. The observed NOEs of H-38/H-42 and $J_{38,39}$ (**27**: 8.9 Hz, **28**: 0 Hz) elucidated the stereochemistries at the C38 and C39 positions of **27** and **28**, respectively. The diene **27** was subjected to ring-closing metathesis with the Hoveyda–Grubbs second-generation catalyst[29] to provide the corresponding cyclized product in 82% yield. Stereoselective hydrogenation of the trisubstituted alkene was performed with the Crabtree catalyst[5e,30,31] to afford **2** as a single stereoisomer. The NOE correlations between H-36 and H-38, which was analyzed by 600 MHz NMR spectroscopy in $CDCl_3$, confirmed the absolute stereochemistry of the 36-methyl substituent to be α.

In conclusion, we have developed a convergent synthetic route to the HIJKLM ring system of ciguatoxin CTX3C. The key transformations were sequential conjugate addition/alkylation, spiroacetalization, intramolecular allylation, ring-closing metathesis, and stereoselective hydrogenation. Further studies toward the total synthesis of ciguatoxin CTX3C are currently underway.

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Supporting Information Available. Experimental procedures, spectroscopic data, structural assignments of selected compounds, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) When we carried out the DIBAL-H reduction at −78 °C or in CH_2Cl_2 as a solvent, only a trace amount of **3** was obtained because the over-reduction occurred as a side reaction.

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