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# Total Synthesis of Ciguatoxin and 51-HydroxyCTX3C

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Ciguatera poisoning is an important medical issue in the tropical and subtropical Pacific and Indian Ocean regions and in the tropical Caribbean.[1] As reef fish are increasingly exported to other areas, it has become a worldwide health problem. Ciguatoxins, the principal causative agents of ciguatera, are produced by an epiphytic dinoflagellate, *Gambierdiscus toxicus*, and transferred to herbivorous and carnivorous fish through the aquatic food chain,[2] at the end of which humans are exposed. Ingestion of affected fish leads to gastrointestinal, cardiovascular, and neurological disorders which may last for weeks or even years. The lethal potency of ciguatoxin [a.k.a. CTX1B (**1**, Scheme 1)] by intraperitoneal injection into mice was reported to be 280 times greater than that of tetrodotoxin.[3] The low fatality rate of ciguatera is due solely to the minute concentration of ciguatoxins in fish flesh.

Since the seminal structural elucidation by Yasumoto in 1989 using 0.35 mg of ciguatoxin **1** extracted from 4000 kg of moray eels (*Gymnothorax javanicus*),[3b,c] more than 20 ciguatoxin congeners have been structurally determined.[4] *G. toxicus* produces less oxidized ciguatoxins that undergo varying extents of oxidations as they pass through the food chain. Interestingly, the more oxygenated forms **1** and **2**[5] are typically 10 times more toxic than the ciguatoxin congeners produced by *G. toxicus* (e.g., CTX3C[6]).[7] This increase in potency amplifies the risk of intoxication in humans.

The very limited supply of ciguatoxins from natural sources has prevented detailed biological studies as well as development of therapeutic methods for ciguatera. Their intriguing and challenging molecular architecture, coupled with this fact, led us to launch a synthetic study, which resulted in the total synthesis of CTX3C in 2001[8] and its second generation synthesis in 2003.[9] Herein, we describe the first total synthesis of the two most toxic members of the ciguatoxin family, ciguatoxin **1** and 51-hydroxyCTX3C **2**, based on our second generation strategy in combination with a newly developed stereo- and chemoselective radical cyclization process.

Ciguatoxins are huge ladder-like polycyclic ethers with the 13 ether rings ranging from five- to nine-membered.[10,11] Despite structural differences in the carbon backbones and their varying oxidation levels, the ciguatoxin congeners share common FG-ring structures.[4] Therefore, our unified convergent strategy was designed to be applicable to all congeners alike: the entire structures were retrosynthetically disconnected at the central portions to afford comparably complex A−E- and H−M-ring systems. In the synthetic direction, it was envisioned that direct formation of key O,S-acetals from the two halves of the molecules, subsequent FG-ring construction, and global deprotection would deliver the oxidized ciguatoxins **1** and **2**. Synthesis of the requisite left and right wing fragments (**3**,[12] **4**,[13] **14**[14]) has been reported previously.

As shown in Scheme 1, total synthesis of 51-hydroxyCTX3C **2** started with assembly of **3** and **4**. Installation of an α-chloride in H−M-ring sulfide **4** was carried out using NCS, leading to α-chlorosulfide **5**. The resulting solution of unstable **5** was directly treated with AgOTf and DTBMP in the presence of A−E-ring alcohol **3**, giving rise to undecacyclic O,S-acetal **6** in 70% yield.[15,16] The TIPS group of the key intermediate **6** was then removed with TBAF to give secondary alcohol **7**, which was converted to methyl acrylate **8a** using methyl propiolate and NMM.[17] By subjecting **8a** to radical cyclization in the presence of *n*-$Bu_3SnH$ and AIBN, the G-ring of **9a** was constructed via 7-exo cyclization with complete control of the two stereogenic centers at C26 and C27. However, the yield of **9a** was modest (40%) due to the concomitant formation of byproduct **10a** via 6-exo cyclization at C23 (20% yield).

The stereo- and chemoselectivity of the radical reaction was reproduced in a model experiment using **23a** (Table 1, entry 1), which represents the central region of the molecule. The exclusive formation of the desired stereoisomer via 7-exo cyclization is explained by the relative stability of the conformation of the corresponding radical intermediate: the C−C bond formation based on the most stable conformation, **25**, leads to the desired product **26** among the four possible stereoisomers.[18] It is possible that the 7-exo/6-exo chemoselectivity of the reaction originates from a balance between SOMO/LUMO interactions and entropic factors. Although there is a stronger interaction between the SOMO of the nucleophilic α-oxy radical and the LUMO of the electron-deficient acrylate than that of the terminal olefin,[19] 6-exo cyclization is entropically favored over its 7-exo counterpart.[20]

The only way to bypass the intrinsic preference for the undesired 6-exo path is to enhance the SOMO/LUMO interaction of the acrylate. Accordingly, the methyl group was replaced with a series of electron-withdrawing functional groups (Table 1, entries 2−4).[21,22] The preference for **26** was found to improve in proportion to the number of fluorides on the phenoxy ring. Remarkably, the simple replacement of Me with pentafluorophenyl enables a 6-fold increase in 7-exo selectivity without affecting stereoselectivity (entry 4).

The new chemoselective radical cyclization was successfully applied to the actual system (Scheme 1). Acrylate **8d** was prepared from **7** using pentafluorophenyl propiolate and $PMe_3$.[23] The radical reaction of **8d** exhibited significantly higher selectivity for 7-exo cyclization (**9e**:**10d** = 10.6:1). As the pentafluorophenyl ester was hydrolyzed in the workup, the product was isolated as carboxylic acid **9e** (74% yield),[24] which was methylated to afford **9a**.

With the 12 ether rings in place, the final steps were construction of the F-ring by ring-closing metathesis (RCM) reaction and deprotection.[25] DIBAL reduction of ester **9a** to the aldehyde, followed by Wittig methylenation, produced pentaene **11**. Upon treatment of **11** with catalytic first-generation Grubbs reagent **13**,[26] only the two terminal olefins were activated, resulting in successful closure of the nine-membered F-ring of **12** in 93% yield. Last,

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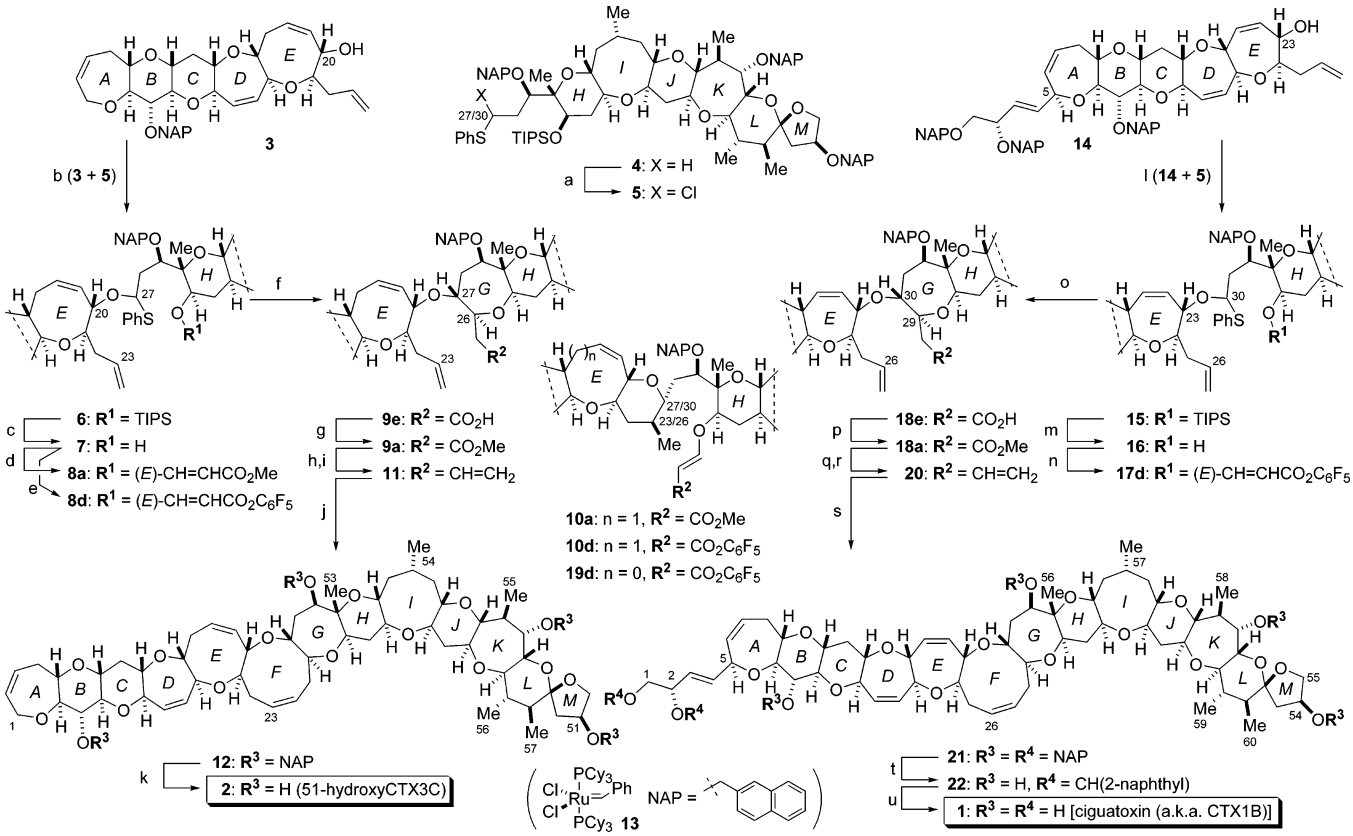
***Scheme 1*** [a]




[a] Reagents and conditions: (a) *N*-chlorosuccinimide (NCS) (1.0 equiv), $CH_2Cl_2/CCl_4$ (1:6), rt; (b) **3** (1.0 equiv), **5** (1.3 equiv), AgOTf (2.5 equiv), di-*tert*-butylmethylpyridine (DTBMP) (5.0 equiv), 4 Å molecular sieves, $CH_2Cl_2/CCl_4$ (5:1), −70 to 0 °C, 70% from **3**; (c) TBAF, THF, 35 °C, 100%; (d) methyl propiolate, *N*-methylmorpholine (NMM), $CH_2Cl_2$, rt, 100%; (e) pentafluorophenyl propiolate, $PMe_3$, $CH_2Cl_2$, rt, 95%; (f) **8a**, *n*-$Bu_3SnH$, 2,2′-azobisisobutyronitrile (AIBN), toluene, 85 °C, **9a**, 40%; **10a**, 20%; **8d**, *n*-$Bu_3SnH$, AIBN, toluene, 85 °C, **9e**, 74%; **10d**, 7%; (g) $TMSCHN_2$, MeOH/benzene (2:5), rt, 87%; (h) DIBAL, $CH_2Cl_2$, −90 °C; (i) $Ph_3PCH_3Br$, *t*-BuOK, THF, 0 °C, 98% (2 steps); (j) **13** (0.2 equiv), $CH_2Cl_2$, 40 °C, 93%; (k) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (10 equiv), $CH_2Cl_2/H_2O$ (2:1), rt, 59%; (l) **14** (1.0 equiv), **5** (1.5 equiv), AgOTf (2.5 equiv), DTBMP (5.0 equiv), 4 Å molecular sieves, $CH_2Cl_2/CCl_4$ (5:1), −70 to 0 °C, 63% from **14**; (m) TBAF, THF, 35 °C, 92%; (n) pentafluorophenyl propiolate, $PMe_3$, $CH_2Cl_2$, rt, 94%; (o) *n*-$Bu_3SnH$, AIBN, toluene, 85 °C, **18e**, 59%; **19d**, 22%; (p) $TMSCHN_2$, MeOH/benzene (2:5), 84%; (q) DIBAL, $CH_2Cl_2$, −90 °C; (r) $Ph_3PCH_3Br$, *t*-BuOK, THF, 0 °C, 77% (2 steps); (s) **13** (0.3 equiv), $CH_2Cl_2$, 40 °C, 78%; (t) DDQ (30 equiv), $CH_2Cl_2/H_2O$ (1:1), rt; (u) 1 N HCl, MeOH, rt, 30% (2 steps).

oxidative removal of the four 2-naphthylmethyl (NAP) groups of **12** using DDQ gave rise to 51-hydroxyCTX3C **2** in 59% yield.[27]

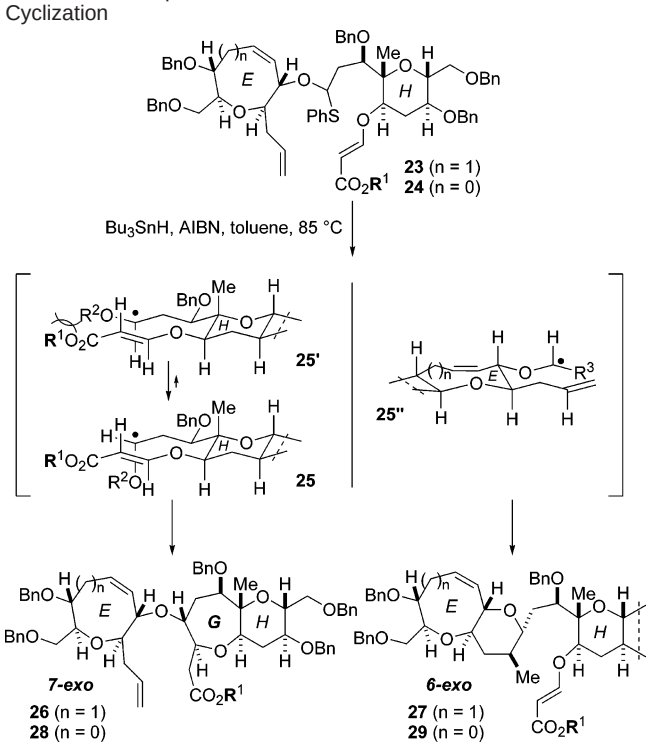
Having established the synthetic route to **2**, our focus next turned to the total synthesis of ciguatoxin **1**. Ciguatoxin **1** not only contains an additional dihydroxybutenyl side chain, but it also possesses a seven-membered E-ring rather than the eight-membered ring of **2**. The synthetic challenge presented by **1** is especially heightened by the presence of the acid/base/oxidant-sensitive bisallylic C5-ether.

A−E-ring alcohol **14** was coupled with α-chlorosulfide **5** by the action of AgOTf in the presence of DTBMP, generating O,S-acetal **15** in 63% yield. The subsequent two steps exchanged the TIPS group of **15** for the pentafluorophenyl acrylate of **17d**. For closure of the G-ring, **17d** was treated with AIBN and *n*-$Bu_3SnH$, selectively producing oxepane **18e** (59% yield) with the desired stereochemistry, along with **19d** as a minor compound (**18e**:**19d** = 2.7:1). The observed 7-exo selectivity was lower than that of **9e** presumably due to the more favorable orientation of the allyl group of the seven-membered E-ring in **17d** for the 6-exo cyclization. Nevertheless, as clearly demonstrated in the model experiment using **24** (Table 1, entries 5 and 6), the pentafluorophenyl group functioned as a selectivity control element regardless of the size of the E-ring, and improved the 7-exo/6-exo chemoselectivity.

Three-step functional group manipulations converted carboxylic acid **18e** to hexaene **20**. The RCM reaction of **20** again demonstrated the high chemoselectivity of the Grubbs catalyst **13** in this highly complex system, affording the fully protected ciguatoxin **21** in 78% yield. DDQ was then used to remove five of the six NAP groups of **21** and simultaneously converted one NAP ether to the 2-naphthylidene acetal at the C1,2-diol, resulting in tetraol **22**. Finally, careful treatment of acetal **22** with acidic conditions delivered ciguatoxin **1** in 30% yield (two steps).

In summary, ciguatoxin **1** and 51-hydroxyCTX3C **2** were synthesized for the first time from the corresponding left and right wing fragments in only 10 and 9 steps, respectively. Synthetic ciguatoxins were determined to be identical in all respects to the naturally occurring form by thin-layer chromatography, HPLC, $^1H$ NMR, and MS.[28] This work proved the high applicability of our unified strategy for construction of highly complex structures with chemically labile functionalities, such as the A-ring side chain of ciguatoxin. Salient methodologies employed in our successful campaign include (i) direct construction of the O,S-acetal; (ii) radical cyclization to form the G-ring; (iii) RCM reaction to form the F-ring; and (iv) an efficient protective group strategy using the NAP group, which can be readily removed under the oxidative conditions. In addition, the discovery that pentafluorophenyl acrylates controlled the reaction path of the radical cyclizations should have wider applications beyond this synthesis. Ciguatoxins prepared here will accelerate biological studies as well as the development of strategies for controlling ciguatera seafood poisoning.

***Table 1.*** Development of Stereo- and Chemoselective Radical Cyclization




| entry | | $R^1$ | *7-exo* : *6-exo* | yield of *7-exo* |
|---|---|---|---|---|
| 1 | **23a** (n = 1) | Me | 2.1 : 1 | 56% (**26a**) |
| 2 | **23b** (n = 1) |  | 3.8 : 1 | 63% (**26b**) |
| 3 | **23c** (n = 1) |  | 5.9 : 1 | 68% (**26c**) |
| 4 | **23d** (n = 1) |  | 12.8 : 1 | 77% (**26e**: $R^1$ = H) |
| 5 | **24a** (n = 0) | Me | 1.2 : 1 | 43% (**28a**) |
| 6 | **24d** (n = 0) |  | 2.6 : 1 | 7% (**28d**)<br>51% (**28e**: $R^1$ = H) |

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**Supporting Information Available:** Experimental procedures and spectroscopic data for synthetic compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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