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Rapid Synthesis of the A–E Fragment of Ciguatoxin CTX3C

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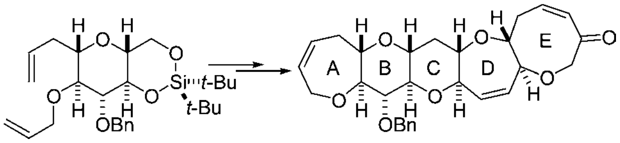
ABSTRACT



The A–E fragment of the marine natural product CTX3C has been prepared in an efficient manner by using a strategy in which two-directional and iterative ring-closing metathesis (RCM) reactions were employed for ring construction.

The ciguatoxins are large fused polyether natural products produced by the marine dinoflagellate *Gambierdiscus toxicus* (Scheme 1).[1] They are the principal causative agents of ciguatera, a severe type of food poisoning that afflicts people in tropical and subtropical regions who have ingested contaminated fish. Thousands of people suffer from ciguatera poisoning each year, exhibiting a range of symptoms that include neurological, gastrointestinal, and cardiovascular effects.[2] In common with other marine polyether toxins, the ciguatoxins bind at site 5 on voltage-sensitive sodium channels.[3] However, they are more potent toxins than structurally related compounds such as the brevetoxins; the relatively low incidence of fatalities associated with cigautera poisoning belies the toxicity of the ciguatoxins and merely reflects the extremely low concentrations that are usually encountered in contaminated fish.

More than 20 ciguatoxins have been isolated from algal and fish sources, and those from the Pacific and Caribbean regions possess molecular structures with distinct differences.[2c] The ciguatoxins produced by the dinoflagellate are also subject to oxidative modification as they are transferred through the food chain and the resulting neurotoxins often possess enhanced potency.[2c]

The size and structural complexity of the ciguatoxins makes them formidable targets. In spite of this, the synthetic allure of the toxins combined with the shortage of natural material available for detailed biological evaluation has encouraged several research groups to embark on total syntheses of members of the ciguatoxin family. This work has culminated in very impressive and elegant total syntheses of CTX3C (**1**), 51-hydroxyCTX3C (**2**), and the parent compound ciguatoxin (**3**) by Hirama and co-workers.[4] These workers have also developed immunoassays for detecting the ciguatoxins using protein conjugates of terminal fragments of the natural products as synthetic haptens.[5]

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(1) (a) Scheuer, P. J.; Takahashi, W.; Tsutsumi, J.; Yoshida, T. *Science* **1967**, *155*, 1267−1268. (b) Yasumoto, T.; Bagnis, R.; Thevenin, S.; Garcon, M. *Nippon Suisan Gakkaishi* . **1977**, *43*, 1015−1019. (c) Yasumoto, T.; Nakajima, I.; Bagnis, R.; Adachi, R. *Nippon Suisan Gakkaishi* **1977**, *43*, 1021−1026.

(2) (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3−18. (c) Lewis, R. J. *Toxicon* **2001**, *39*, 97−106. (d) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228−242.

(3) Dechraoui, M.-Y.; Naar, J.; Pauillac, S.; Legrand, A.-M. *Toxicon* **1999**, *30*, 125−143.

(4) (a) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904−1907. (b) Inoue, M.; Miyazaki, K.; Uehara, H.; Maruyama, M.; Hirama, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12013−12018. (c) Inoue, M.; Hirama, M. *Acc. Chem. Res.* **2004**, *37*, 961−968. (d) Inoue, M.; Miyazaki, K.; Ishihara, Y.; Tatami, A.; Ohnuma, Y.; Kawada, Y.; Komono, K.; Yamashita, S.; Lee, N.; Hirama, M. *J. Am. Chem. Soc.* **2006**, *128*, 9352−9354.

(5) (a) Tsumuraya, T.; Fujii, I.; Inoue, M.; Tatami, A.; Miyazaki, K.; Hirama, M. *Toxicon* **2006**, *48*, 287−294. (b) Nagumo, Y.; Oguri, H.; Tsumoto, K.; Shindo, Y.; Hirama, M.; Tsumuraya, T.; Fujii, I.; Tomioka, Y.; Mizugaki, M.; Kumagai, I. *J. Immunol. Methods* **2004**, *289*, 137−146. (c) Oguri, H.; Hirama, M.; Tsumuraya, T.; Fujii, I.; Maruyama, M.; Uehara, H.; Nagumo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7608−7612.

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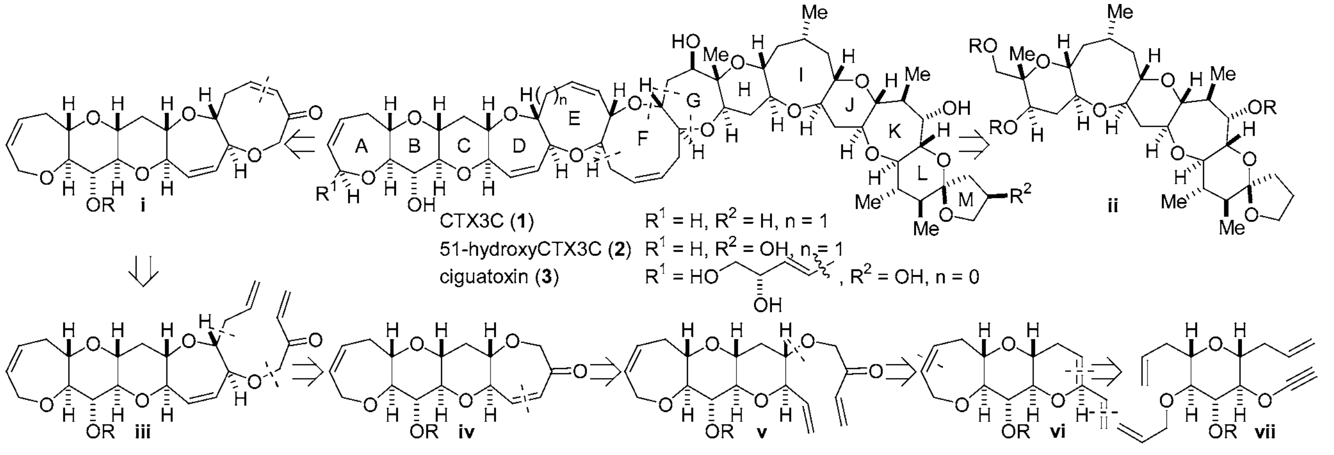
Scheme 1

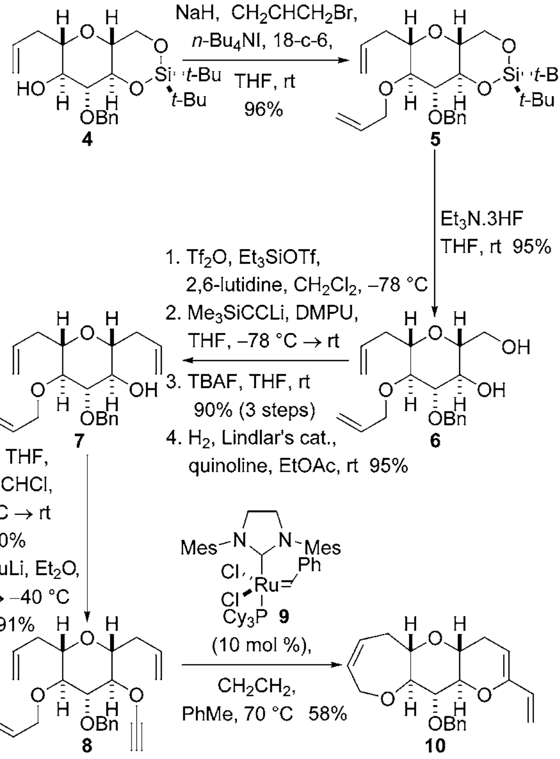


As part of a large program directed toward the development of a general strategy for the total synthesis of marine polyethers, we have embarked on a total synthesis of CTX3C (**1**).[6] Herein, we disclose a relatively short and efficient approach to the synthesis of the pentacyclic ABCDE fragment of CTX3C in which two-directional and iterative RCM reactions are used to effect ring construction.[7]

Our retrosynthetic analysis of ciguatoxin CTX3C (**1**) commences with disconnection through rings F and G, dividing the target into two fragments (**i** and **ii**) of similar size and complexity (Scheme 1). Disconnection of the A−E fragment **i** by alkene scission in the E ring leads to the tetracyclic system **iii**. Cleavage of the enone side chain at the ether linkage, removal of the allyl group, and alcohol oxidation gives the A−D fragment **iv**. Scission of the alkene in ring D then produces the tricyclic unit **v**. Cleavage of the ether side chain and dehydration delivers the diene **vi**, which after simultaneous A and C ring opening by a retrosynthetic double RCM disconnection gives the B ring fragment **vii** (Scheme 1).

The initial target was the tricyclic ABC fragment, corresponding to **vi** in the retrosynthetic analysis, which was to be prepared by simultaneous ring closure of the A and C rings.[7f] Preparation of the cyclization precursor **8** commenced with conversion of the alcohol **4** into the allyl ether **5** and subsequent cleavage of the di-*tert*-butylsilylene group (Scheme 2).[7f] The resulting diol **6** was then subjected to one-pot triflate and triethylsilyl ether formation followed by triflate displacement with lithium trimethylsilyl acetylide in the presence of DMPU. Desilylation of both hydroxyl groups followed by selective and high-yielding partial hydrogenation of the alkyne with Lindlar's catalyst in the presence of quinoline afforded the triene **7**. The desired two-directional RCM precursor **8** was then obtained in good yield by alkynylation of the free hydroxyl group, using the procedure first developed by Greene and co-workers,[8] and used by us during the construction of related fused polyethers.[7c,g,h] Simultaneous diene and enyne RCM to form the A and C rings was accomplished by treatment of substrate **8** with the ruthenium complex **9** under an atmosphere of ethene (Scheme 2).[9] The fused tricyclic ether **10** was obtained in a rather modest 58%

Scheme 2



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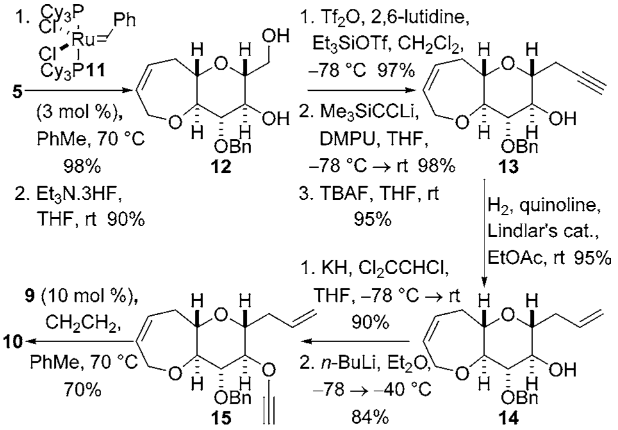
[6] Clark, J. S. *Chem. Commun.* **2006**, 3571−3581.

[7] (a) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123−126. (b) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127−130. (c) Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *Chem. Commun.* **1998**, 2629−2630. (d) Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321−8324. (e) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231−8248. (f) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372−374. (g) Clark, J. S.; Elustondo, F.; Trevitt, G. P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, *58*, 1973−1982. (h) Clark, J. S.; Elustondo, F.; Kimber, M. C. *Chem. Commun.* **2004**, 2470−2471. (i) Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157−6162.

yield and efforts to increase the yield by optimization of the double RCM reaction were not successful.

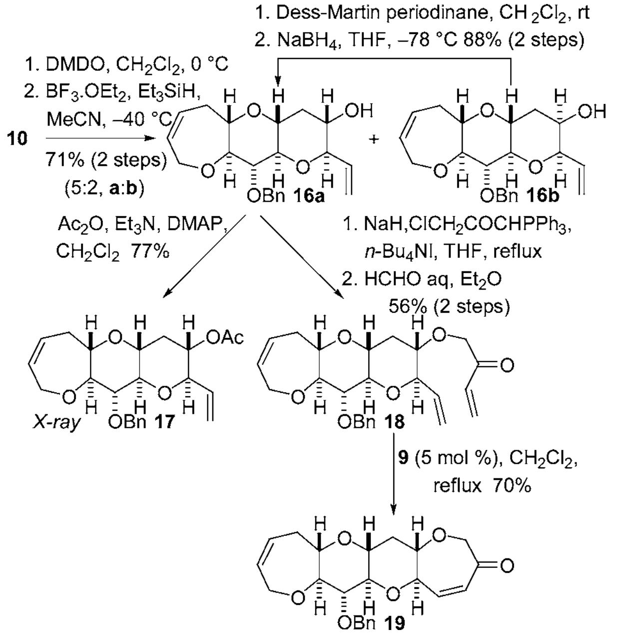
Scheme 3



Sequential construction of the A and C rings was also explored (Scheme 3). Formation of the A ring was achieved by RCM of the allyl ether **5**, using the ruthenium complex **11**.[9a] Removal of the di-*tert*-butylsilylene group then afforded the diol **12** in excellent yield. From this stage onward, the route was analogous to that used to prepare the double RCM precursor **10** (Scheme 2). One-pot triflate and triethylsilyl ether formation followed by triflate displacement with lithium trimethylsilyl acetylide in the presence of DMPU and subsequent desilylation delivered the alkyne **13**. Partial hydrogenation of the alkyne with Lindlar's catalyst in the presence of quinoline afforded the alcohol **14**, which was then converted into the corresponding alkynyl ether **15**.[8] Enyne RCM with use of the complex **9** in the presence of ethene delivered the fused tricyclic ether **10** in 70% yield.

Although the yield of the tricyclic ether **10** obtained from RCM reaction of the alkynyl ether **15** is higher than that obtained from double RCM of the precursor **8**, the routes shown in Schemes 2 and 3 are found to be of similar efficiency when both the yield and the number of steps are considered. Operationally, however, it was easier to scale up the route shown in Scheme 3 to produce gram quantities of the required tricyclic ether **10**.

Scheme 4



The efficient synthesis of the tricyclic ABC fragment **10** meant that construction of the D and E rings could be explored. Formation of the D ring began with selective epoxidation of the electron-rich enol ether in compound **10**, using dimethyldioxirane at 0 °C. The reaction delivered an unstable mixture (5:2 ratio) of diastereomeric epoxides that was used in the subsequent step without purification (Scheme 4). Regioselective reduction of this mixture of vinylic epoxides proved to be challenging and several reducing agents and sets of reaction conditions were screened before the transformation could be performed in a reliable manner. The best results were obtained when the mixture of epoxides was treated with triethylsilane in the presence of boron trifluoride etherate in acetonitrile at −40 °C. Under these reaction conditions, the diastereomeric alcohols **16a** and **16b** were obtained in 71% yield from the diene **10**. To confirm the stereochemical outcome of the reaction, the crystalline acetate **17** was prepared from the major alcohol diastereoisomer **16a**. X-ray analysis of the acetate **17** revealed that the alcohol **16a** possessed the required configuration at both the vinyl- and hydroxyl-bearing stereogenic centers. Oxidation of the minor alcohol **16b** by using the Dess−Martin protocol and reduction of the resulting ketone with sodium borohydride afforded the alcohol **16a**, which had been obtained during reductive opening of the mixture of anomeric epoxides. This result shows that reduction of the 5:2 mixture of epoxides delivers the correct configuration at the vinyl-bearing stereogenic center irrespective of the stereochemistry of the anomeric epoxide, i.e., reduction of each of the two oxocarbenium ions obtained from the epoxide mixture occurs from the same face giving products with the required configuration at the allylic ether stereogenic center.

Construction of the D and E rings with RCM of enone precursors was now explored. Following procedures described by Cossy et al.[10] and employed by us in a recent synthesis of the tetracyclic core of hemibrevetoxin B,[11] the hydroxyl group of the tricyclic alcohol **16a** was alkylated with triphenylchloroacetonylphosphorane (Scheme 4).[12] Treatment of the resulting ylide with formaldehyde in diethyl ether

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(8) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919−2922.

(9) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

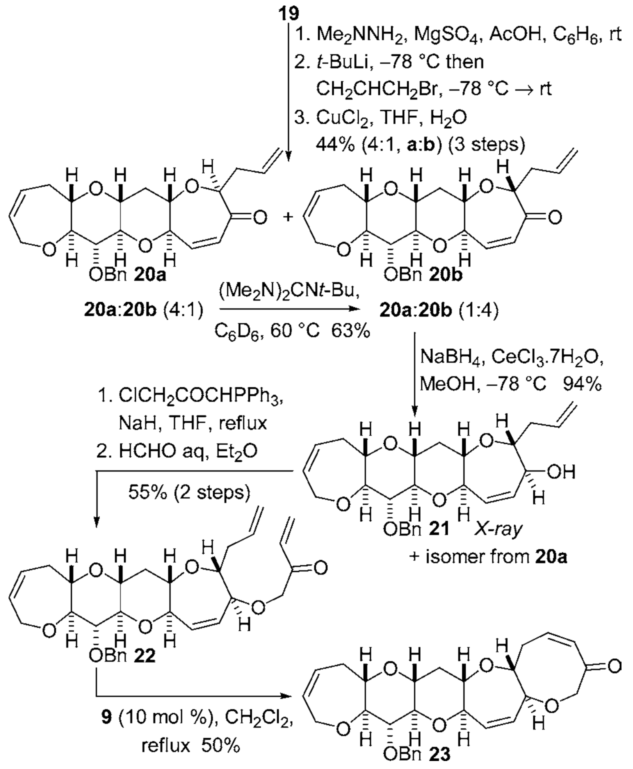
(10) Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263−7266.

(11) Clark, J. S.; Grainger, D. M.; Ehkirch, A. A.-C.; Blake, A. J.; Wilson, C. *Org. Lett.* **2007**, *9*, 1033−1036.

then provided the enone **18** in 56% yield over two steps. Construction of ring D was then accomplished by treatment of the enone **18** with the ruthenium complex **9**, giving the required ABCD system **19** in 70% yield (Scheme 4).

Attachment of the eight-membered E ring to the A−D fragment **19** was accomplished by using the sequence of enone formation and RCM that had been employed to construct the D ring (Scheme 5). Construction of the E-ring commenced with introduction of an allyl group. Previous studies performed in our group had demonstrated that it was not possible to effect direct deprotonation and enolate alkylation of 4-oxapen-3-one systems related to the enone **19**, and that it was necessary to convert the ketone into a hydrazone prior to enolate generation.[11] The ketone **19** was therefore converted into the corresponding *N*,*N*-dimethylhydrazone. Sequential deprotonation of the hydrazone, enolate alkylation, and hydrazone cleavage then produced a 4:1 mixture of the alkylated ketones **20a** and **20b** in reasonable yield. ^{1}H NMR NOE experiments revealed that the major product was the diastereoisomer **20a** possessing incorrect configuration at the newly created sterogenic center. The ketone **20a** was epimerized by treatment with 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base)[13] to give mainly the required isomeric compound **20b** (1:4 ratio, **20a**:**20b**). Reduction of the mixture of enones **20a** and **20b** (1:4) using standard Luche conditions then gave the crystalline allylic alcohol **21** in good yield. X-ray analysis of this compound confirmed its structure and also established that the configurations of all eight stereogenic centers matched those in the A−D fragment of the natural product. The remaining enone-containing side chain was then installed in the same way as before (cf. **16a** → **18**, Scheme 4) to afford diene **22** in 55% yield over two steps. Completion of the A−E fragment of CTX3C was accomplished by RCM of the enone **22** mediated by the complex **9**, which delivered the eight-membered cyclic ether and produced the pentacyclic system **23** in 50% yield.

Scheme 5



In summary, the pentacyclic A−E fragment of CTX3C has been synthesized in 21 steps from the alcohol **4**, which is prepared from commercially available tri-*O*-acetal-D-glucal.[7f] Efficient assembly of the A−C fragment was achieved by using a two-directional double RCM reaction. The D and E rings were then constructed by elaboration of the A−C fragment by using an iterative side chain introduction and enone RCM protocol.

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Supporting Information Available: Spectroscopic and other data for the key compounds **10**, **16a**, **16b**, **17**, **18**, **19**, **21**, **22**, and **23**, plus X-ray data (CIF files) for compounds **17** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Hudson, R. F.; Chopard, P. A. *J. Org. Chem.* **1963**, *28*, 2446−2447.

(13) (a) Barton, D. H. R.; Elliott, J. D.; Géro, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085−2090. (b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737−752.