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Two Convergent Routes to the Left-Wing Fragment of Ciguatoxin CTX3C Using *O*,*S*-Acetals As Key Intermediates

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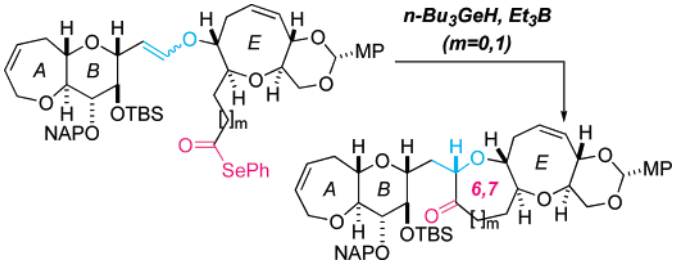
ABSTRACT



Ciguatoxins, principal causative toxins of ciguatera seafood poisoning, are large ladderlike polycyclic ethers. Here, we report two convergent routes to synthesis of the multiolefinic left half of ciguatoxins based on a newly developed acyl radical strategy. Remarkably, only 13 steps from the monocyclic E-ring were required to construct the left wing.

Ciguatoxins [e.g., CTX3C (**1**)[1] and 51-hydroxyCTX3C (**2**)[2] in Figure 1] were isolated as the toxic components of the widespread seafood poisoning known as ciguatera.[3] One of its most characteristic features is reversal of thermal sensation; touching cold water typically causes pain similar to that of an electric shock. It also can cause other symptoms such as diarrhea, vomiting, muscle pain, and itching. More than 400 species of fish can be vectors of ciguatoxins, but the presence of these toxins in fish is unpredictable. To detect **1** and **2** from fish samples, we recently developed a sandwich enzyme-linked immunosorbent assay (ELISA), which used anti-ciguatoxin antibodies produced against the synthetic left and right halves of ciguatoxins.[4]

Our total syntheses of **1** and **2** involved coupling between the left and right wings with subsequent construction of the central ring system (blue highlighting in Figure 1).[5] Therefore, the partial ciguatoxin structures are important as haptens

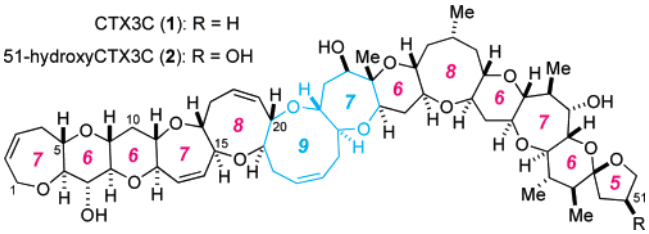


Figure 1. Structures of ciguatoxins.

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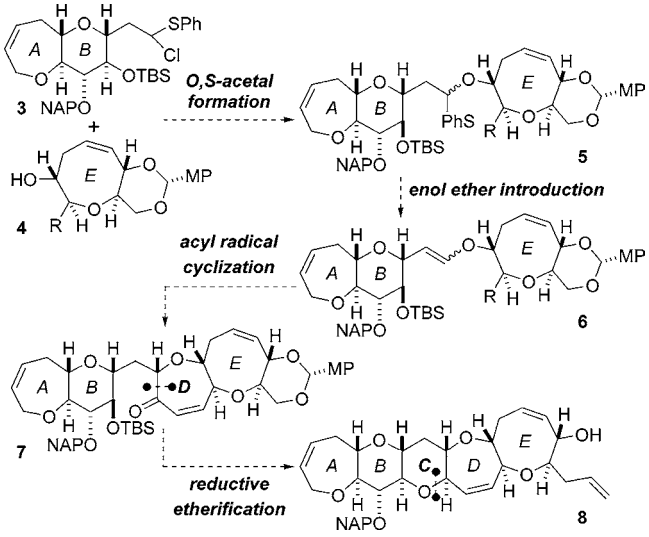
for preparing anti-ciguatoxin antibodies and as fragments for the practical total synthesis. This prompted us to develop an improved synthetic route to the pentacyclic left wing fragment of **1** and **2**.[6,7]

The synthesis design for the left half **8** was based on recently developed acyl radical methodology (Scheme 1).[8,9]

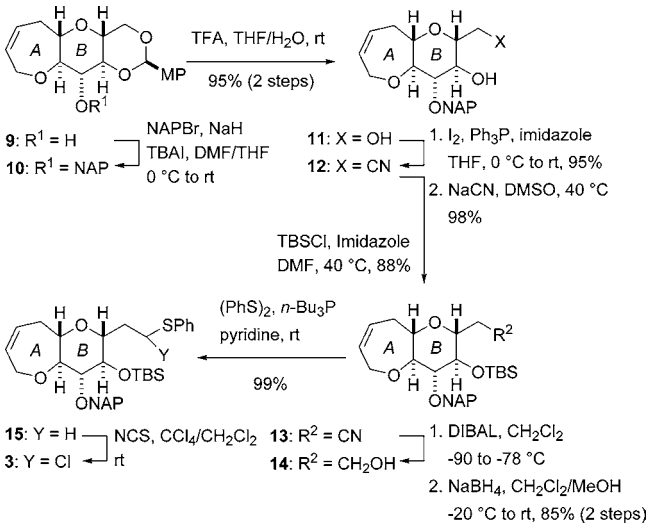
Scheme 1. Synthesis Plan of the Left-Wing Fragment of Ciguatoxins



We previously applied the intermolecular alkylation of an ester enolate of the E-ring fragment to the AB-ring iodide to synthesize **8**.[6a] In contrast to these strong basic conditions, the present coupling of the AB- and E-ring fragments (**3** and **4**) was based on a neutral reaction linking the C−O bond as the *O*,*S*-acetal **5**.[10] After *O*,*S*-acetal formation, the Ag^{+}-induced elimination of the sulfide from **5** would produce enol ether **6**, the acyl radical addition to which would cyclize the ether ring of **7**.[11] Then, the six-membered C-ring of **8** was planned to be constructed through reductive etherification. A series of these mild reactions were designed to simplify the functional group manipulations of the highly oxygenated intermediates and consequently to shorten the synthetic routes in comparison to the previous schemes.

First, the requisite AB-ring moiety **3** was prepared from known compound **9**[6a] (Scheme 2). The secondary alcohol

Scheme 2. Synthesis of the AB-Ring Fragment



of **9** was converted to 2-naphtylmethyl (NAP) ether **10**,[12] the acetal of which was removed under acidic conditions, leading to diol **11**. A reagent combination of I_2, PPh_3, and imidazole[13] chemoselectively transformed the primary alcohol of **11** into the iodide, and subsequent cyanide introduction gave the one-carbon homologated product **12**. After TBS protection of **12**, stepwise reduction of nitrile **13** using DIBAL and $NaBH_4$ resulted in alcohol **14**. Finally, treatment of **14** with $(PhS)_2$ and *n*-Bu_3P[14] generated phenylsulfide **15**, and the chloride was subsequently introduced into the α-position of the sulfide by the action of NCS to afford **3**.[15]

To investigate the structural effect of R in **16** on the efficiency of the acyl radical cyclization, side chains of the E-ring fragments were varied; namely, the R groups of **4a**, **4b**, and **4c** have two sp^2-, two sp^3-, and one sp^3-carbons, respectively, with the methoxycarbonyl terminus (Scheme

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(7) For syntheses of the BCDE, ABCD, or ABCDE ring part of ciguatoxins from other groups, see: (a) Kira, K.; Isobe, M. *Tetrahedron Lett*. **2001**, *42*, 2821. (b) Fujiwara, K.; Koyama, Y.; Kawai, K.; Tanaka, H.; Murai, A. *Synlett* **2002**, 1835. (c) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889. (d) Fuwa, H.; Fujikawa, S.; Tachibana, K.; Takakura, H.; Sasaki, M. *Tetrahedron Lett*. **2004**, *45*, 4795. (e) Fujiwara, K.; Goto, A.; Sato, D.; Ohtaniuchi, Y.; Tanaka, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett*. **2004**, *45*, 7011.

(8) Inoue, M.; Ishihara, Y.; Yamashita, S.; Hirama, M. *Org. Lett.* **2006**, *8*, 5801.

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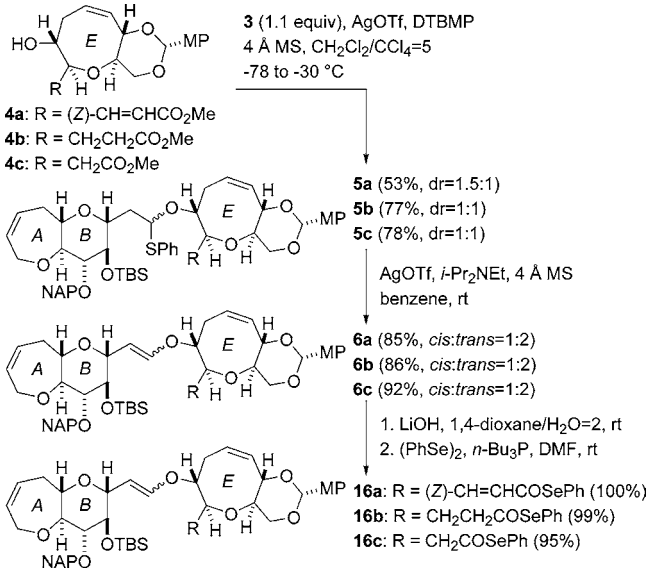
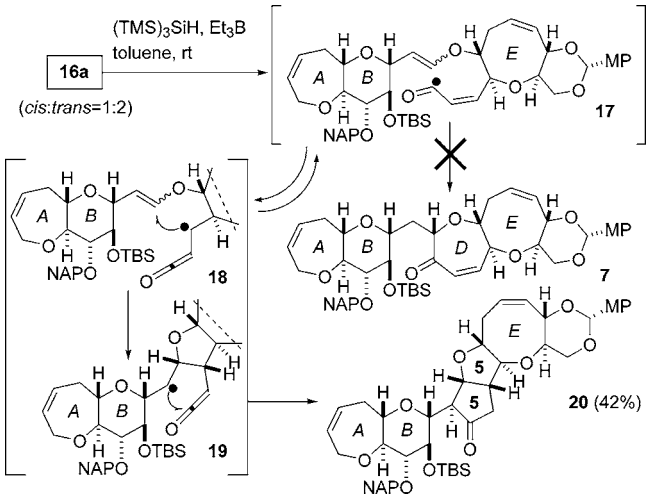
Scheme 3. Synthesis of Three Cyclization Substrates



3).[16] Each of the compounds **4a**−**c** was subjected to the four-step protocol to furnish cyclization substrates **16a**−**c** in high yield. Coupling between α-chlorosulfide **3** and the hindered secondary alcohol **4** was promoted by AgOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to generate the coupling adduct **5** as a diastereomeric mixture.[5,10,17] The sulfide of **5** then was activated by the same silver salt in the presence of Hünig base, resulting in effective formation of chemically labile enol ether **6** as a mixture of geometric isomers.[8] The methyl ester of **6** was transformed into the phenylselenyl ester of **16** via saponification and subsequent treatment with $(PhSe)_2$ and *n*-Bu_3P.[18]

As shown in Scheme 4, single-step construction of the unsaturated D-ring of **7** from **16a** was first attempted. Surprisingly, treatment of **16a** with $(TMS)_3SiH$ and Et_3B in toluene at room temperature produced only the 5/5-ring

Scheme 4. Unsuccessful Attempt to Construct the D-Ring



system **20** as a single isomer. The three-dimensional structure of **20** including the newly formed three stereocenters was determined by NOESY experiments and coupling constants (see Supporting Information). This outcome was attributable to the slower 7-exo cyclization of acyl radical **17** in comparison to the 5-exo cyclization of its tautomer **18**. Resultant formation of alkyl radical **19** then was followed by the second 5-exo cyclization to yield **20**.[19] Despite the failure to generate **7**, the stereoselective tandem radical cyclization of α,β-unsaturated selenoesters is potentially applicable to the related oxabicyclo[3.3.0]octane ring systems.

Next, we examined the six-membered ring cyclizations of the nonconjugated selenoester **16c** (Scheme 5). As expected, the $(TMS)_3SiH/Et_3B$-mediated radical reaction[20] of **16c** led to formation of tetrahydropyran **23** and its epimer **22** in 65% combined yield along with aldehyde **21** (11%).[21] The undesirable path to **21** via direct reduction of the acyl radical was suppressed successfully by replacing $(TMS)_3SiH$ with the poorer hydrogen donor *n*-Bu_3GeH,[22] resulting in formation of a diastereomeric mixture of **22** and **23** in 79% yield (**22**/**23** = 1:1.5). The stereogenic center of the chromatographically separated **22** was epimerized efficiently using DBU to afford **23** (**22**/**23** = 1:2). Then, **23** was subjected to three reactions to construct the requisite unsaturated seven-membered D-ring. Trimethylsilyldiazomethane in the presence of Me_3Al induced the ring expansion of six-membered **23**, resulting in seven-membered α-silyl ketone **26**.[23] Subsequent [1,3]-silyl migration[24] was accomplished by heating **26** to 140 °C to afford TMS enol ether **27**, which was converted to the requisite α,β-unsaturated ketone **7** by Saegusa oxidation.[25]

A more efficient route to **7** was developed using **16b**, a one-carbon homologue of **16c** (Scheme 5). The combination

(16) Compounds **4a**−**c** were synthesized by standard functional group transformation from the previously reported E-ring fragment (ref 6a).

(17) McAuliffe, J. C.; Hindsgaul, O. *Synlett* **1998**, 307.

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(19) Related tandem radical cyclizations were reported by Pattenden. (a) Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 271. (b) Hayes, C. J.; Herbert, N. M. A.; Harrington-Frost, N. M.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 316. (c) De Boeck, B.; Harrington-Frost, N. M.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 340.

(20) Evans successfully applied these reaction conditions to construction of the five-, six-, and seven-membered ether rings through acyl radical addition to vinylogous carbonates and sulfonates: (a) Evans, P. A.; Roseman, J. D. *J. Org. Chem.* **1996**, *61*, 2252. (b) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880. (c) Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **1997**, *38*, 8165. (d) Evans, P. A.; Manangan, T. *J. Org. Chem.* **2000**, *65*, 4523. (e) Evans, P. A.; Raina, S.; Ahsan, K. *Chem. Commun.* **2001**, 2504.

(21) The increased ratio of the *trans*-isomer of aldehyde **21** (*cis*:*trans* = 1:11) implied the more efficient cyclization of the *cis*-isomer of **16c**. For the discussion on cyclization efficiency of the geometric isomers, see ref 8.

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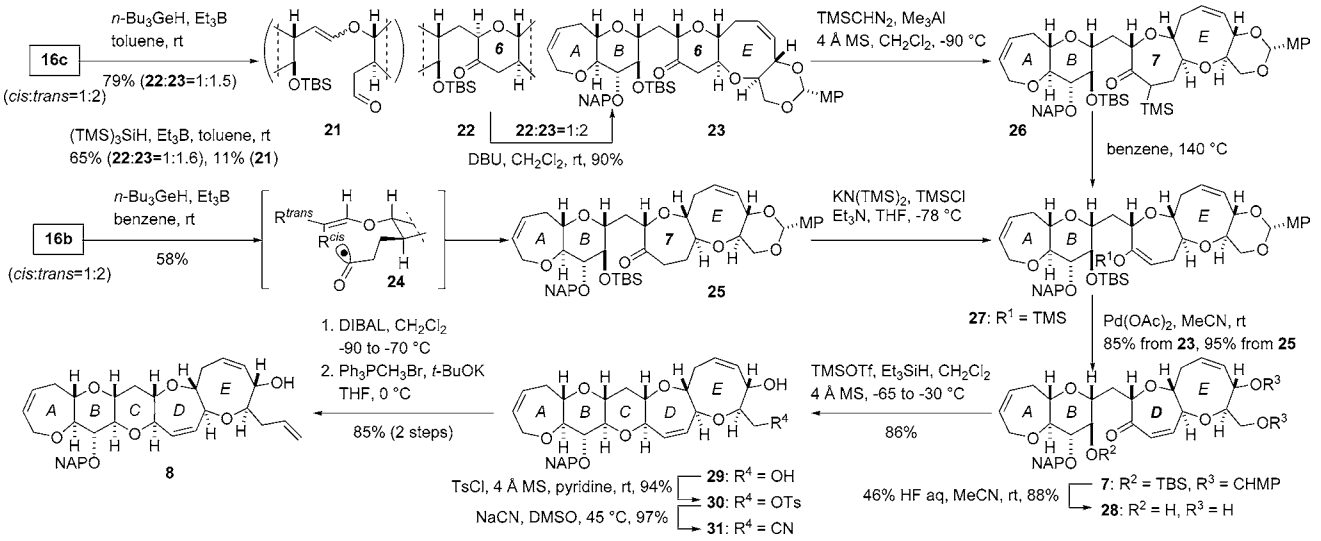
(25) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

Scheme 5. Two Synthetic Routes to the Left-Wing Fragment of Ciguatoxins



of *n*-Bu_3GeH and Et_3B effectively cyclized **16b** into oxepane **25** as the sole isomer in 58% yield. This excellent stereocontrol is in contrast to the modest diastereocontrol obtained for six-membered cyclization from **16c** and is ascribed to the strongly favored transition state conformation of **24**, in which the $A^{1,3}$-strain is minimized. Although the distinct stereochemical outcome of **16b**/**c** is not completely understood, specific formation of the desired isomer **25** from **16b** facilitated the synthesis. Regioselective TMS enol ether formation from **25**, followed by Pd^{2+}-mediated oxidation, gave rise to the appropriately functionalized D-ring **7**. Overall, facile intramolecular addition of nucleophilic acyl radicals to the electron-rich enol ethers in the presence of the two intrinsically more reactive disubstituted olefins in **16b**/**c** demonstrated the power and the generality of our convergent strategy.[26]

Having constructed the D-ring, the final steps involved C-ring formation and carbon-chain extension. The protective groups of **7**, with the exception of NAP, were removed with aqueous hydrogen fluoride to afford triol **28**. Then, reductive etherification[27] of hydroxy ketone **28** using TMSOTf and Et_3SiH established the last stereocenter via axial attack of the hydride on the oxonium cation intermediate, yielding tetrahydropyran **29**. The primary alcohol of diol **29** was tosylated to give **30**, which was treated with sodium cyanide to afford **31**. Last, DIBAL reduction of nitrile **31** to the aldehyde and subsequent Wittig methylenation delivered the left-wing fragment **8**.

In summary, we have developed two acyl radical routes to the ABCDE ring system **8** of ciguatoxins. The results demonstrated the high applicability of this convergent strategy for construction of multiolefinic structures. Remarkably, the half ciguatoxin structure was assembled in only 13 steps from the AB-ring fragment **3** (22% overall yield via **16b**), whereas 21 steps (6.3%)[6a] or 35 steps (4.3%)[6b] were previously required from the coupling. The left-wing fragment prepared here will facilitate the practical total synthesis of ciguatoxins and the preparation of antibodies for controlling ciguatera seafood poisoning.

Acknowledgment. This work was supported financially by SORST, Japan Science and Technology Agency (JST), and a Grant-in-Aid for Scientific Research (S) from the Japan Society for the Promotion of Science (JSPS).

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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