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Stereoselective synthesis of the left wing of Caribbean ciguatoxin

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This paper is dedicated to Professor Satoshi Ōmura on the occasion of the 2010 Tetrahedron Prize

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ABSTRACT

Ciguatoxins, the principal causative toxins of ciguatera seafood poisoning, are potent toxic polycyclic ethers. In this paper, we report a stereoselective and secure route to the left wing of Caribbean ciguatoxin on the basis of a 6-*exo* radical cyclization strategy.

1. Introduction

Ciguatera seafood poisoning, an important medical issue in tropical and subtropical regions, causes gastrointestinal, cardiovascular, and neurological disorders that may last for weeks or even years.[1] Alhough ciguatera had been localized to the islands of the Pacific Ocean, Indian Ocean, and the Caribbean Sea, it has become a global problem due to expanding tourism and trade. Ciguatoxins (CTXs), the principal causative toxins of ciguatera, are ladder-like polycyclic ethers 3 nm in length with ring sizes ranging from five- to nine-members.[2] Ciguatoxins exhibit their potent toxicities (LD_{50}=0.25–4 μg/kg, mice) by binding to the voltage-sensitive sodium channels (VSSC) of excitable membranes.[3,4] Recent progress in analytical technology reveals that the ciguatoxins are structurally varied according to geographical region.[5] Caribbean ciguatoxin C-CTX-1 (**1**, Fig. 1) was isolated from the carnivorous fish horse-eye jack (*Caranx latus*) as the main toxin of ciguatera in the Caribbean Sea.[5a] In contrast to the typical Pacific ciguatoxins, CTX3C (**2**) and 51-hydroxyCTX3C (**3**),[6] **1** possesses 14 ether rings with a more complicated architecture.

We have successfully synthesized three Pacific ciguatoxins (**2**, **3**, and CTX1B)[7] and developed a sandwich enzyme-linked immunosorbent assay (ELISA) for their detection.[8,9] Moreover, we have reported the syntheses of ABCDE-,[10] M-,[11] and LMN-ring[12] fragments of **1**. However, more practical and secure methods to prepare sufficient amounts of the fragments are still required for the total synthesis of **1**. Recently, we developed three efficient routes for constructing *trans*-fused polyethers based on radical

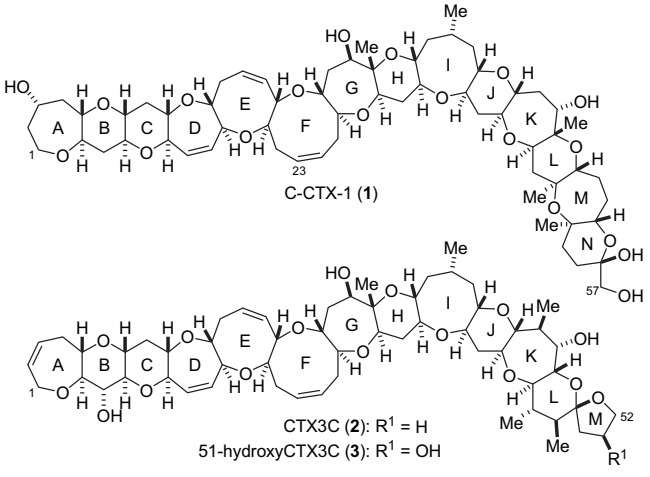

Fig. 1. Structures of ciguatoxins.

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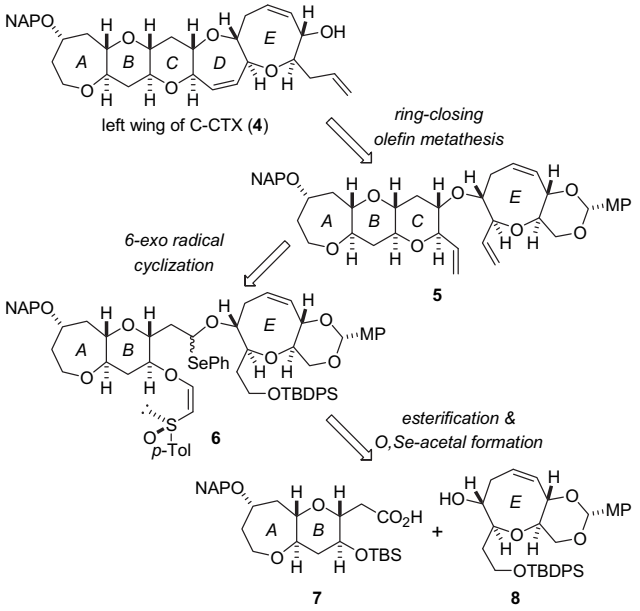
reactions: (i) an acyl radical cyclization/reductive etherification sequence,[13] (ii) a 7-*exo* radical cyclization using an electron-deficient acrylate/ring-closing olefin metathesis (RCM) sequence,[7,14] and (iii) a 6-*exo* radical cyclization using a *cis*-vinyl sulfoxide/RCM sequence.[7h] Herein, we describe an advanced synthetic route to the left wing of **1** utilizing method (iii) as the key strategy.

2. Results and discussion

A new synthesis plan of the left wing (**4**) of **1** is summarized in Scheme 1. The seven-membered D-ring was retrosynthetically cleaved to triene **5**, which could be generated from *O*,*Se*-acetal **6** by the key 6-*exo* radical cyclization. The intermediate **6** would be prepared from bicycles **7** and **8** via esterification and *O*,*Se*-acetal formation.

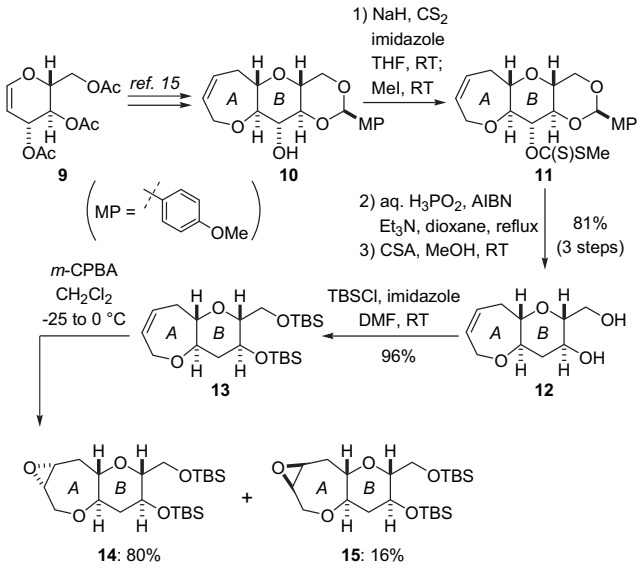


Scheme 1. Retrosynthesis of the left wing of C-CTX-1 (**1**).

We first improved the synthesis of the AB-ring of C-CTX-1 from the known alcohol **10**, which was prepared from tri-*O*-acetyl-D-glucal **9** (Scheme 2).[15] Deoxygenation of the B-ring alcohol of **10** was achieved by Barton radical reduction.[16] Successive treatment of **10** with NaH, carbon disulfide, and MeI afforded xanthate **11**. Removal of xanthate by the action of aqueous phosphinic acid and AIBN in the presence of Et_3N in dioxane furnished the C-CTX-1 type B-ring. Subsequent acid treatment to cleave the anisylidene acetal moiety provided diol **12** in 81% overall yield from **10**. After TBS protection of the two hydroxy groups of **12**, epoxidation of the resulting TBS ether **13** with *m*-CPBA in CH_2Cl_2 at low temperature afforded α-epoxide **14** in 80% yield along with its diastereomer **15** (16%).

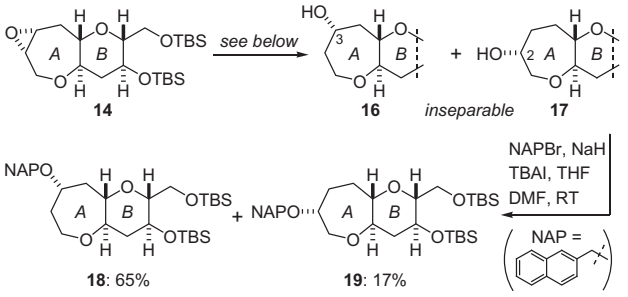
Reductive opening of epoxide **14** was explored as summarized in Table 1. Treatment of **14** with lithium triethylborohydride ($LiBHEt_3$) gave an inseparable 1:1 mixture of the desired C3-alcohol **16** and its regioisomer **17** in 95% yield (entry 1). L-Selectride [$LiBH(s\text{-}Bu)_3$], Red-Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$], and DIBAL gave unsatisfactory results (entries 2–4). After considerable experimentation we eventually found that treatment of **14** with $LiAlH_4$ in Et_2O at −30 to −20 °C provided **16** as the major product (4:1) in 100% combined yield. The secondary alcohols, **16** and **17**, were protected as 2-naphthylmethyl (NAP)[7b,17] ethers to give **18** and **19**, which were isolated in 65% and 17% yields, respectively.

Selective cleavage of the less-hindered TBS ether of **18** was achieved by exposure to CSA in MeOH at 0 °C to give primary



Scheme 2. Synthesis of epoxide **14**.

Table 1
Regioselective cleavage of epoxide **14**



Entry	Conditions	Combined Yield	**16**:**17**[a]
1	$LiBHEt_3$, THF, −20 °C	95%	1:1
2	$LiBH(s\text{-}Bu)_3$, THF, −20 °C to RT	41%	1:1
3	Red-Al,THF, −20 to 0 °C	17%	1:1
4	DIBAL, CH_2Cl_2, 0 °C	decomposed	–
5	$LiAlH_4$, Et_2O, −30 to −20 °C	100%	4:1

[a] The ratio of **16**:**17** was determined by ^{1}H-NMR analysis

alcohol **20** (Scheme 3). Following the method developed by Sammuelsson,[18] the hydroxy group of **20** was converted to the iodide **21** in 93% yield from **18**. After the one carbon homologation of **21** by substitution of iodide with sodium cyanide, nitrile **22** was transformed to the carboxylic acid **7** through DIBAL reduction and Pinnick oxidation in 85% overall yield from **21**. The TES-protected AB-ring carboxylic acid **24** was also prepared from **7** in two steps.

As shown in Scheme 4, the AB-ring carboxylic acid **7** was condensed with the E-ring alcohol **8**[7h] by Yamaguchi esterification[19] to afford ester **25a**. The ester was treated with DIBAL in CH_2Cl_2 at −90 °C followed by acetylation with Ac_2O and DMAP to produce acetate **26a** of the hemiacetal.[20] The acetate group of **26a** was substituted with the phenylselenyl group by the action of $i\text{-}Bu_2AlSePh$, which was freshly prepared from DIBAL and $(PhSe)_2$,[21] to give *O*,*Se*-acetal **27a** in 57% yield. Although selective removal of the TBS group of **27a** was attempted, cleavage of the TBDPS ether always occurred competitively. We thus examined protection of the primary alcohol of the corresponding diol **28**. Although a variety of experimental conditions was tested, including treatment of **28** with