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A convergent synthesis of the right-hand fragment of ciguatoxin CTX3C

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ABSTRACT

A convergent synthesis of the right-hand fragment of ciguatoxin CTX3C was investigated. The first and second generation stereocontrolled syntheses of the LM ring fragment were achieved via spiroacetalization as a key step, respectively. The polyether framework of the HIJKLM ring fragment was constructed in a convergent manner by using intramolecular allylation, ring-closing metathesis, and stereoselective hydrogenation to form the 36-methyl substituent as the key transformations.

1. Introduction

Various biologically and physiologically active secondary metabolites have been isolated from marine origin.[1] In particular, polyether and polyol marine natural products with a large molecular weight, such as brevetoxins, maitotoxin, and palytoxins are some of the most attractive molecules for natural product chemists, synthetic chemists, biochemists, and pharmacological scientists due to their extraordinary structures and significant biological activities.[2]

Ciguatera is a food poisoning caused by eating toxic specimens of normally edible fishes in tropical and subtropical areas.[3] Ciguatera poisoning has affected a large and diverse population in previously non-endemic regions due to the increase of tourism and international trade in seafood from tropical region. The research report in 2010 shows that the global number of poisonings is estimated to be 50,000–500,000 cases annually.[4]

Ciguatoxin CTX3C (**1**, Scheme 1) was isolated from cultured dinoflagellate *Gambierdiscus toxicus* by Yasumoto's group and was found to be one of the causative toxins of ciguatera poisoning.[5] This molecule exhibits potent neurotoxicity [LD_{50} (mouse, ip): 1.3 μg/kg] by binding to the voltage-sensitive sodium channels. The chemical structure of **1**, which possesses ladder-shaped 13 ether rings and 30 stereogenic centers, was elucidated on the basis of the COSY, TOCSY, and NOESY spectra by using 0.7 mg specimen obtained from 1100 L of the culture. Its structural complexity and biologically important activities[4] have attracted much attention from the synthetic chemists as the target molecule.[6,7] Previously, we synthesized the left-hand ABCDE ring fragment of **1**, stereoselectively.[8] In this full account, we report the development of the convergent synthetic route to the right-hand HIJKLM ring fragment of **1**, the useful synthetic intermediate toward the total synthesis of **1**.[9]

2. Results and discussion

2.1. Retrosynthetic analysis

Our retrosynthetic analysis of **1** is illustrated in Scheme 1. Previously, we reported a convergent method for the construction of the polycyclic ether frameworks via intramolecular allylation and subsequent ring-closing metathesis.[10] On the basis of this method, the polycyclic framework of **1** was broken down into the left-hand ABCDE ring fragment **2** and the right-hand HIJKLM ring fragment **3**. The IJ ring moiety of **3** could be constructed by applying the same procedure to allylic stannane **4**. The cyclization precursor **4** could be synthesized by esterification of alcohol **5** and carboxylic acid **6**. The KLM ring system **6** could be synthesized from the LM ring system **7**, of which the carbon framework could be constructed via stereoselective spiroacetalization and installation of the methyl substituent at the C48 position of ketone **8**.[11]

2.2. Synthesis of the H ring system

First, we investigated the stereoselective synthesis of the H ring system (Scheme 2). Benzyl protection of known alcohol **9**[12] followed by ozonolysis and two-carbon elongation with a Wittig reagent gave α,β-unsaturated ester **10**. After the ester **10** was reduced

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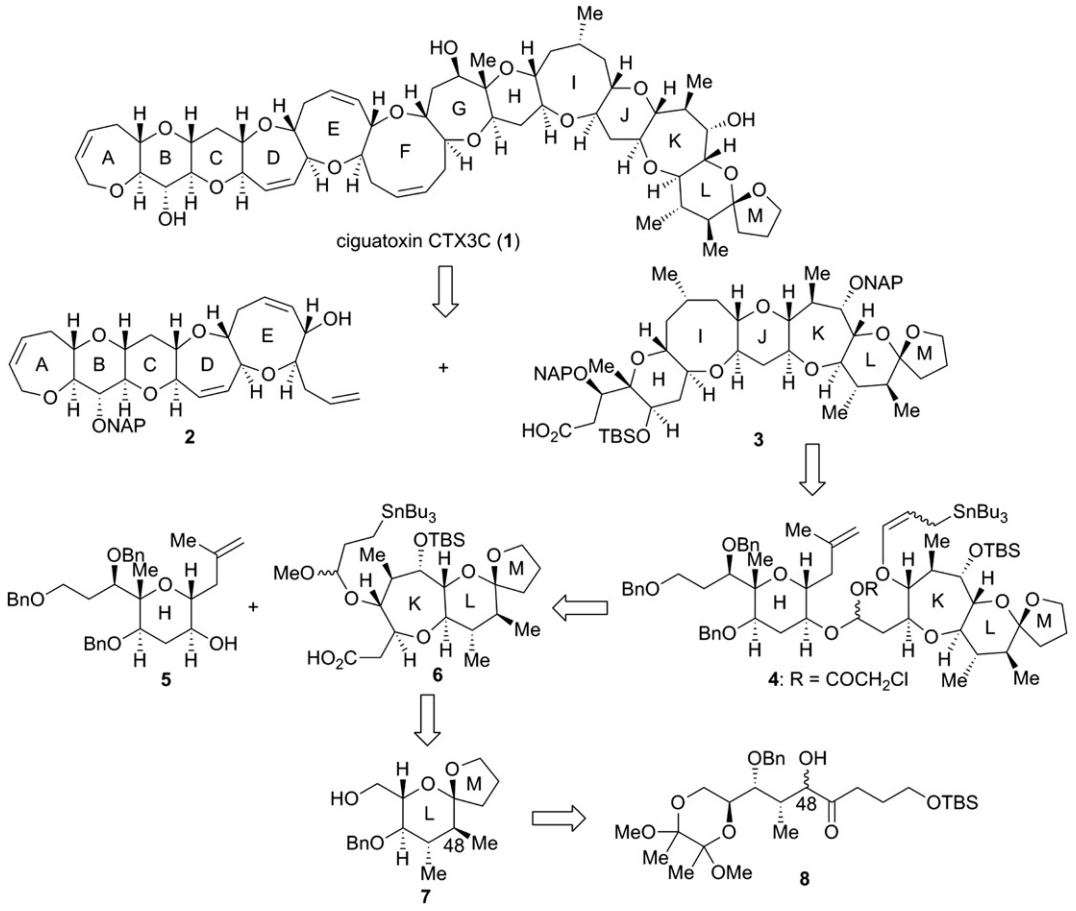
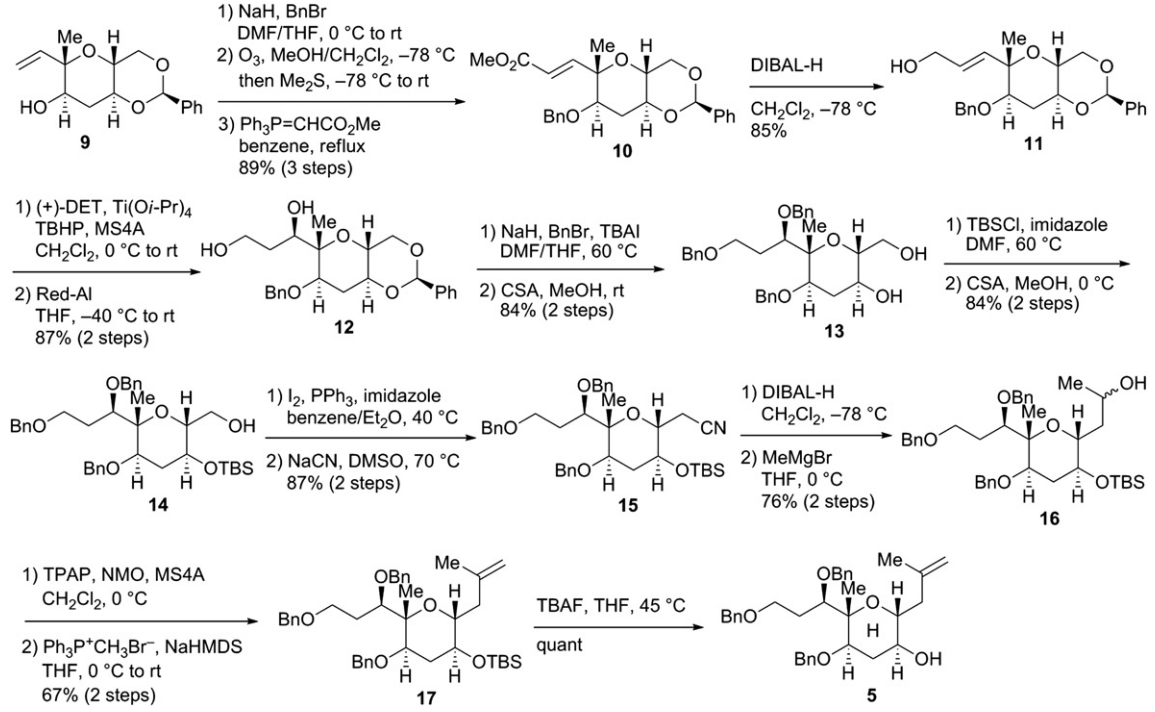


Scheme 1. Structure and retrosynthetic analysis of ciguatoxin CTX3C (**1**).



Scheme 2. Synthesis of the H ring system **5**.