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Synthesis of the FGH Ring Fragment of Ciguatoxin

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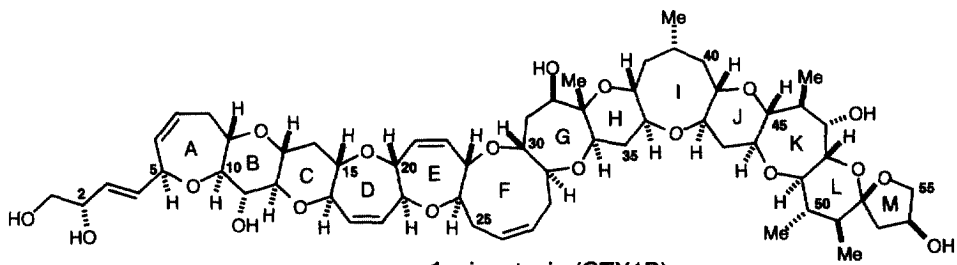
Abstract:

Stereoselective synthesis of the FGH ring fragment of ciguatoxin is described. The key steps in the present synthesis are an intramolecular radical cyclization to construct oxepane ring G and ring-closing metathesis reaction to construct hexahydrooxonin ring F.

Key words: metathesis; oxepanes; polyethers; radicals and radical reactions

Ciguatoxin (CTX1B, **1**) and its congeners, naturally occurring polycyclic ethers originated in marine unicellular algae, are the principle toxins associated with ciguatera fish poisoning [1-3]. These potent neurotoxins reportedly bind to the same site of voltage-sensitive sodium channels as brevetoxins, another class of structurally related marine toxins [4]. The structural complexity and exceptionally potent neurotoxity of the ciguatoxins together with their scarcity from natural sources make them the prime target for a total synthesis [5-14]. In the course of our synthetic efforts toward ciguatoxin and its simplified analogues [15,16], we recently reported a new efficient method for the construction of *O*-linked oxepane ring system by an intramolecular radical cyclization [17]. In this letter, we report a successful application of this strategy to a more highly functionalized system leading to a convergent synthesis of the FGH ring fragment **2** of ciguatoxin by its combination with a ring-closing metathesis reaction [18].



1: ciguatoxin (CTX1B)

Retrosynthetically, we planned to construct the hexahydrooxonin ring F in **2** from the precursor diene **3** by ring-closing metathesis reaction, which has been successfully applied to the synthesis of medium-sized ether ring system [10,13,14,19-22] (Scheme 1). The *O*-linked oxepane ring G in **3** could in turn be accessible from β-alkoxyacrylate **4** with the aid of our previously developed radical cyclization strategy [17].

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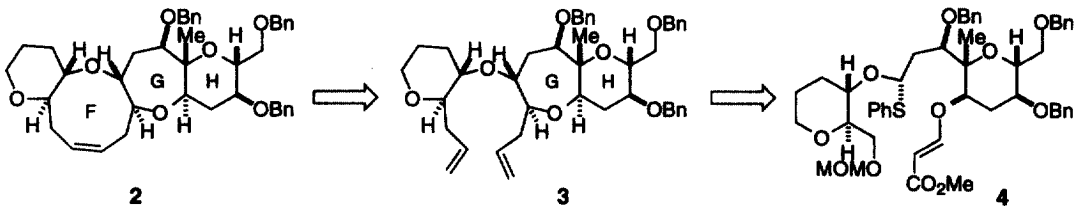
Scheme 1



2 3 4

The synthesis of β-alkoxyacrylate **4** was started with a three-step routine conversion of the known alcohol **5** [23] into triisopropylsilyl (TIPS) ether **6** in 84% overall yield (Scheme 2). Oxidative cleavage of the double bond followed by chelation-controlled addition of allyltri-*n*-butyltin [24] and benzylation provided olefin **7** as a single diastereomer in 81% overall yield. Another oxidative cleavage of the double bond and subsequent addition of diol **8** to the resulting β-benzyloxyaldehyde in the presence of $Sc(OTf)_3$ [25,26] afforded acetal **9** as a single isomer in 80% overall yield. Treatment of **9** with Et_2AlSPh [27] effected selective cleavage of the acetal C-O bond and monothioacetal **10** was obtained as a single diastereomer in 79% yield.[1] Use of Et_2AlSPh in this reaction instead of the previously used *i*-$Bu_2AlSePh$ [17] resulted in a higher yield and better reproducibility. Protection of the primary alcohol as its MOM ether followed by removal of the silyl group and treatment with methyl propiolate and *N*-methylmorpholine provided β-alkoxyacrylate **4** (87% overall yield), which was subjected to an intramolecular radical cyclization reaction. Namely, treatment of a 10 mM solution of **4** in toluene with a catalytic amount of AIBN and 10 equiv of *n*-Bu_3SnH at 80 °C gave the *O*-linked oxepane **11** in 85% yield. The desired stereochemistry of **11** was confirmed on the basis of $^3J_{H,H}$ and NOE data as shown in Figure 1.

Elaboration of **11** to the ciguatoxin FGH ring fragment **2** is outlined in Scheme 3. DIBAL reduction of **11** to the aldehyde and Wittig methylenation gave olefin **12** in 77% yield. Selective removal of the MOM group (83%) followed by triflate formation and subsequent treatment with lithium trimethylsilylacetylide [28] provided silylacetylene **13** (61% yield for the two steps), which upon desilylation and partial hydrogenation afforded diene **3**. Ring-closing metathesis reaction of **3** (4 mM in CH_2Cl_2) using Grubbs catalyst **14**

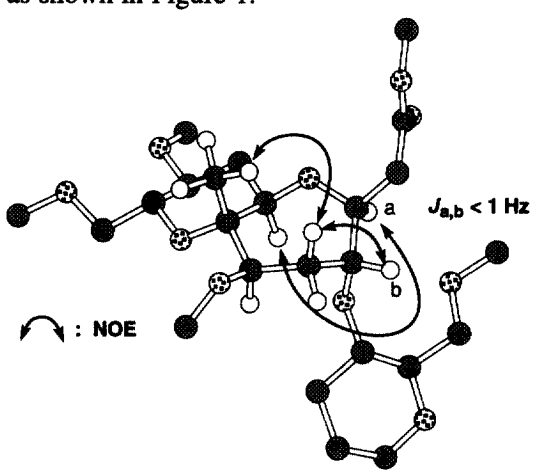
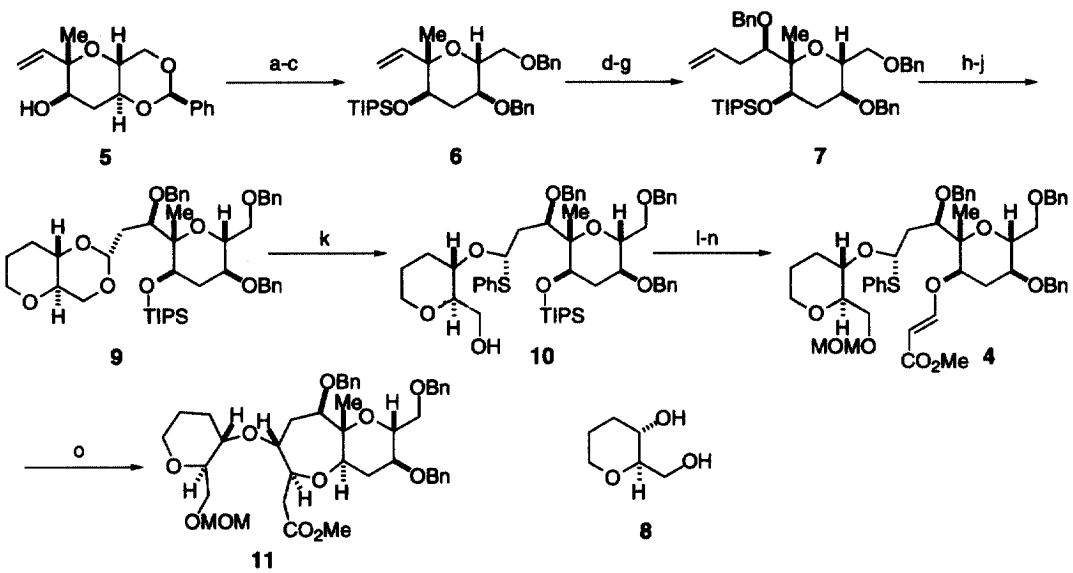


Figure 1

[1]The configuration of the sulfide of **10** was assumed on the basis of the reaction mechanism, see: reference 17.

Scheme 2



Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; (b) CSA, CH_2Cl_2-MeOH, r.t.; (c) NaH, BnBr, DMF, r.t., 84% (3 steps); (d) OsO_4, NMO, acetone-H_2O (5:1), r.t.; (e) $NaIO_4$, THF-H_2O (5:1), r.t.; (f) allyltri-*n*-butyltin, $MgBr_2$·OEt_2, CH_2Cl_2, -78 to 0 °C; (g) NaH, BnBr, DMF, r.t., 81% (4 steps); (h) OsO_4, NMO, acetone-H_2O (4:1), r.t.; (i) $NaIO_4$, THF-H_2O (2:1), r.t.; (j) **8**, $Sc(OTf)_3$, PhH, r.t., 80% (3 steps); (k) Et_2AlSPh, CH_2Cl_2-hexane (1:2), r.t., 79%; (l) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, r.t.; (m) *n*-Bu_4NF, THF, r.t., 99% (2 steps); (n) *N*-methylmorpholine, methyl propiolate, CH_2Cl_2, r.t., 88%; (o) *n*-Bu_3SnH, AIBN (cat.), $PhCH_3$ (10 mM), 80 °C, 85%.

[29] at 35 °C for 4 days resulted in the formation of the hexahydrooxonin ring to provide the targeted FGH ring fragment **2** in 61% yield.

The ^1H and ^{13}C NMR signals due to the hexahydrooxonin ring of **2** were severely broadened at room temperature, as previously reported for ciguatoxin [1] and our model compounds furnished with its F ring [15,16].

The synthetic strategy described herein provides a possible solution to a convergent construction of ciguatoxin framework at this position. Further synthetic studies toward ciguatoxin and their designed analogs are currently underway.

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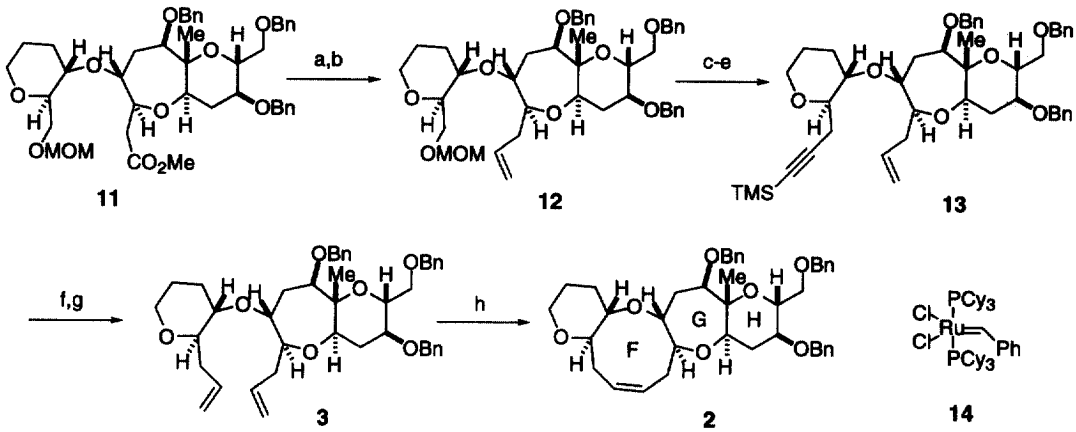
Scheme 3



Reagents and conditions: (a) DIBAL, CH_2Cl_2, -78 °C; (b) $Ph_3PCH_3^+Br^-$, NaHMDS, THF, 0 °C, 77% (2 steps); (c) BF_3·OEt, Me_2S, CH_2Cl_2, 0 °C, 83%; (d) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C; (e) (trimethylsilyl)acetylene, *n*-BuLi, HMPA, THF, -78 °C, 61% (2 steps); (f) K_2CO_3, MeOH-THF (3:2), r.t., 90%; (g) H_2, Lindlar cat., EtOAc, r.t., 86%; (h) **14**, CH_2Cl_2 (4 mM), 35 °C, 4 days, 61%.

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