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Convergent and Stereoselective Method for Synthesis of *O*-Linked Oxepane Ring System by Intramolecular Radical Cyclization

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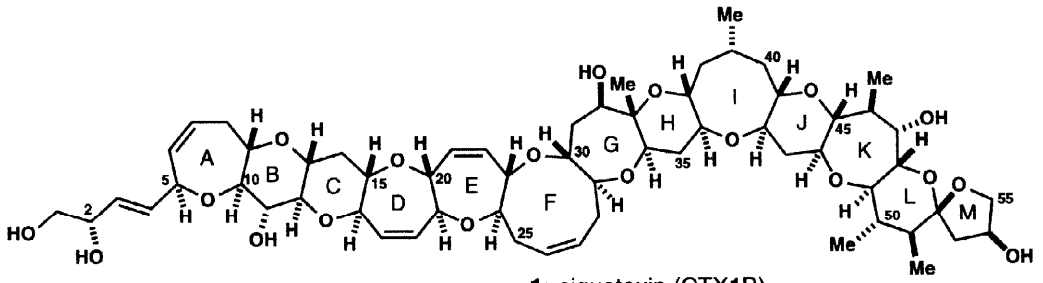
Abstract: A new strategy for the construction of *O*-linked oxepane ring system is described. The present method involves regioselective acetal cleavage by *i*-$Bu_2AlSePh$ and intramolecular radical cyclization by use of β-alkoxyacrylate. © 1998 Elsevier Science Ltd. All rights reserved.

Ciguatoxin (CTX1B, **1**) and its congeners, naturally occurring polycyclic ethers originating from marine unicellular algae, are principle toxins for ciguatera fish poisoning[1,2] and reportedly bind to the same site of voltage-sensitive sodium channels (VSSC) as brevetoxins, another class of structurally related marine toxins.[3] Their structural complexity and exceptionally potent neurotoxity, as well as their scarcity from natural sources, make them the prime target for total synthesis.[4] In the course of our synthetic efforts toward ciguatoxin and its simplified analogues,[5] it was necessary to develop a convergent and efficient method for the assembly of large polycyclic ether arrays. We recently reported that a *trans*-fused 9-membered ether ring system, corresponding to the ring F of ciguatoxin, could be assemebled efficiently from an *O*-linked oxacyclic ring system, which was constructed by an intramolecular reaction of γ-alkoxyallylsilane with acetal.[5d,e] However, an *O*-linked bisoxepane system with the correct *trans-syn-trans* stereochemistry could not be obtained by this method.[6] In order to circumvent this problem, an alternative method for the construction of an *O*-linked oxepane ring system was required. In this communication, we describe a new efficient method for the construction of *O*-linked oxepane ring system **2** by an intramolecular radical cyclization.



1: ciguatoxin (CTX1B)

A number of radical methods by use of β-alkoxyacrylate as radical acceptors have been recently developed for the stereoselective construction of five- to seven-membered cyclic ethers in an iterative manner.[7] However, convergent strategy based on the radical reaction have not yet been reported. Our synthetic strategy for the construction of *O*-linked oxepane ring system is outlined in Scheme 1. We envisioned obtaining oxepane ring in

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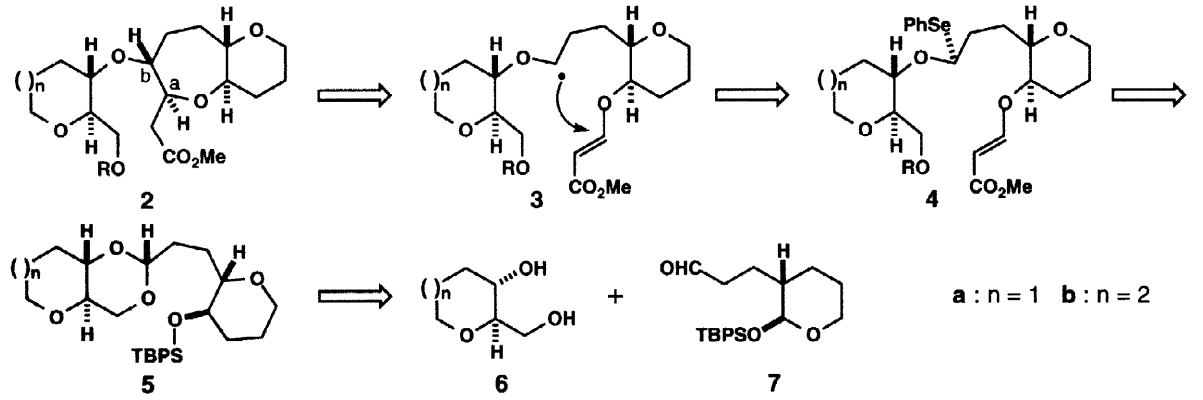
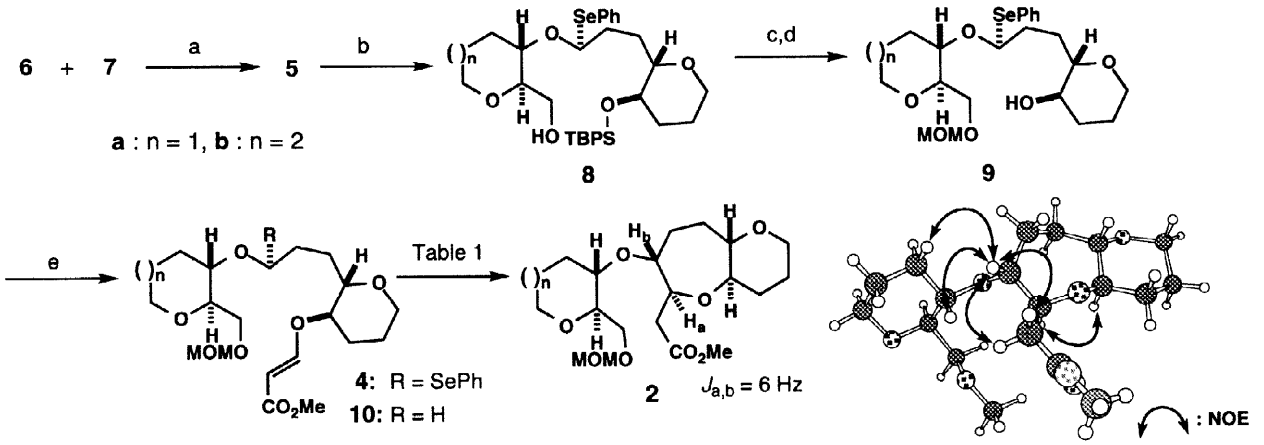
O-linked oxacycle **2** by an intramolecular reaction of α-alkoxyalkyl radical **3**, generated from monoselenoacetal **4**. In this radical reaction, the stereochemical outcome at C-a was predicted to afford the desired configuration by the literature precedents,[7] but the stereochemistry of C-b could not be easily predicted. In turn, the monoselenoacetal moiety in **4** would be introduced by regioselective cleavage of the acetal ring in **5**, which should be easily prepared from diol **6** and aldehyde **7**.

Scheme 1



Feasibility of this approach, namely, the synthesis and cyclization of **4a** was thus investigated first. The synthesis started with reaction of diol **6a** with aldehyde **7** in the presence of camphorsulfonic acid (CSA), giving acetal **5a** as a single stereoisomer in quantitative yield (Scheme 2). Upon treatment of **5a** with diisobutylaluminum phenylselenide (*i*-$Bu_2AlSePh$)[8] in toluene at -20 °C, regioselective cleavage of the acetal C-O bond occurred to yield monoselenoacetal **8a** as a single stereoisomer in 94% yield.[9] Presumably, this reaction proceeds by a tight ion paired S_N1-like mechanism, which involves regioselective complexation of the organoaluminum reagent to the more sterically accessible dioxane oxygen followed by intramolecular attack of the phenylselenide anion *syn* to the cleaved C-O bond.[9] Protection of the hydroxyl group in **8a** as its methoxymethyl ether and removal of the silyl group provided alcohol **9a**, which was then treated with methyl propiolate in the presence of tributylphosphine[10] to give the requisite β-alkoxyacrylates **4a**.

Scheme 2



Reagents and conditions: (a) CSA, PhH, 80 °C (**5a**: quant, **5b**: 72%); (b) *i*-$Bu_2AlSePh$, $PhCH_3$, -20 °C (**8a**: 94%, **8b**: 92%); (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt; (d) *n*-Bu_4NF, THF, rt (**9a**: 91%, **9b**: 88% for 2 steps each); (e) methyl propiolate, Bu_3P, CH_2Cl_2, rt (**2a**: 76%, **2b**: 91%).

The key intramolecular radical cyclization of **4a** was then investigated and the results are summarized in Table 1. Treatment of a solution of **4a** and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) in toluene with *n*-Bu_3SnH (2 equiv) at 105 °C provided an inseparable 1.2:1 mixture of the desired *O*-linked oxepane **2a** and the reduction product **10a** in 76% yield (entry 1). Formation of the reduction product was avoided by keeping the *n*-Bu_3SnH concentration low by slow addition via syringe pump over 4- to 5-h period and the ratio of **2a**:**10a** was improved to 10:1 (entry 2). The yield of **2a** was further improved by carring out the reaction with triethylborane[11] in place of AIBN at room temperature, giving a 10:1 mixture of **2a** and **10a** in 80% combined yield (entry 3). Under the high dilution conditions, the similar result was obtained (entry 4). The stereochemistry of **2a** was determined by $^3J_{H,H}$ data and NOE experiments. Radical cyclization of **4b**, prepared from diol **6b** and **7** (Scheme 2), was also effected to give the desired *O*-linked oxepane **2b** together with a small amount of the reduction product **10b** in a ratio of 10:1 and 87% combined yield (entry 5).

Table 1

entry	substrate	conditions	Yield [%]	(**2**:**10**)
1	**4a** (30 mM)	*n*-Bu_3SnH (2 equiv), AIBN (cat.), toluene, 105 °C	75	(1.2:1)
2	**4a** (10 mM)	*n*-Bu_3SnH (2 equiv), AIBN (cat.), toluene, 105 °C[a]	61	(10:1)
3	**4a** (10 mM)	*n*-Bu_3SnH (2 equiv), Et_3B (cat.), benzene, r.t.[a]	80	(10:1)
4	**4a** (1 mM)	*n*-Bu_3SnH (2 equiv), Et_3B (cat.), benzene, r.t.	82	(10:1)
5	**4b** (1 mM)	*n*-Bu_3SnH (2 equiv), Et_3B (cat.), benzene, r.t.	87	(10:1)

[a]Dropwise addition of *n*-Bu_3SnH via syringe pump over 4 to 5 h.

The present method was next applied to the formation of *O*-linked tetrahydropyran ring system (Scheme 3). β-Alkoxyacrylate **12** was synthesized from diol **6a** and aldehyde **11** by the same sequence of reactions as described in Scheme 2 and subjected to the radical cyclization under the optimal conditions. Contrary to the case of cyclization of **4**, *O*-linked oxacycle **13** with a *cis*-relationship between the newly generated two stereogenic centers was obtained in 66% yield. The stereochemical outcome of these radical reactions may be rationalized by the transition state conformers **A** and **B**, respectively, in which steric congestion between the bulky alkoxy group attached to the radical center and acrylate unit are avoided (Figure 1).

Scheme 3

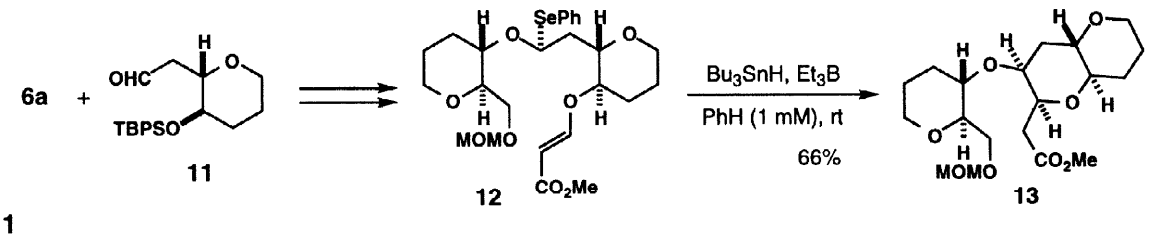
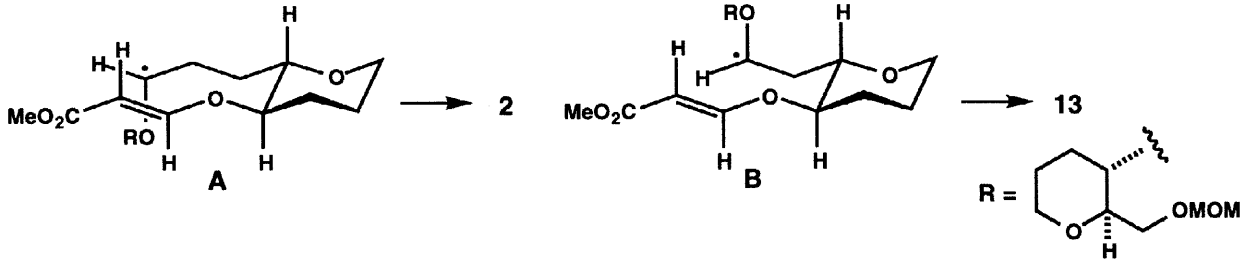


Figure 1



In conclusion, a highly convergent and stereoselective method for the synthesis of *O*-linked oxepane ring system has been developed. The new strategy described herein provides the basis for the synthesis of the DEFGH ring system of ciguatoxin. Further synthetic studies along this line are currently underway.

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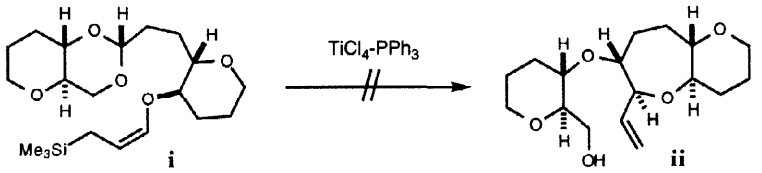

i **ii**

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