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Construction of Fused Oxonene Ring and Reproduction of Conformational Behavior Shown by Ring F of Ciguatoxin

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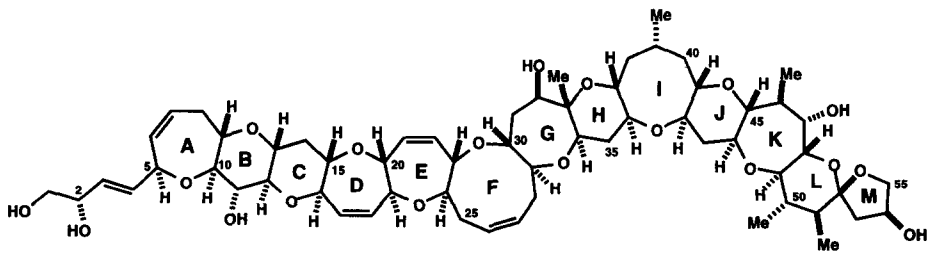
Abstract: *trans*-Fused 6-9-6 tricyclic ether **2** was synthesized and conformational alternation of the oxonene ring was reproduced as was observed for that in the ciguatoxin molecule (ring F). SmI_2-promoted intramolecular Reformatsky reaction of *O*-linked bicyclic compound **4** features the construction of an oxonane ring in the present synthesis.

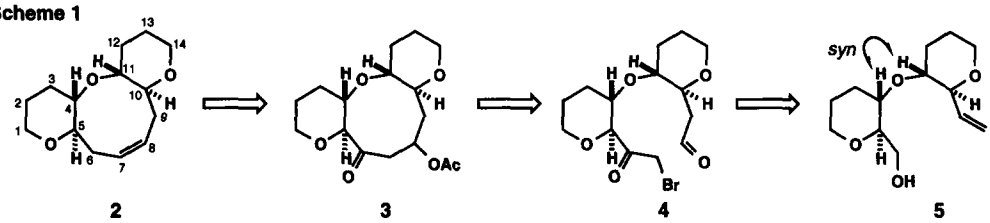
Ciguatoxin (CTX1B, **1**) and its congeners play a most important role in ciguatera fish poisoning.[1,2] The toxin is one of the most potent neurotoxins known to date and reportedly binds to the same site of voltage-sensitive sodium channels (VSSC) as brevetoxins, another class of structurally related marine toxins.[3] The ciguatoxin molecule consists of 12 *trans*-fused cyclic ethers ranging from six- to nine-membered, where another five-membered oxacycle is spirally attached at one end. The most remarkable structural feature is that oxonene ring F in the central region of the molecule undergoes a conformational change in solution. Thus, ring F functions as a hinge in conformational flexibility of the molecule, which is speculated to play an important role in its binding to VSSC.[4] From the synthetic point of view, construction of the oxonene ring system is a formidable and challenging synthetic objective due to severe difficulties caused by unfavorable entropy factors as well as transannular interactions.[5] In this communication, we describe the first achievement in synthesis of *trans-syn-trans* 6-9-6 tricyclic system **2** in the course of our synthetic efforts toward ciguatoxins[6] and also conformational alteration of thus constructed oxonene ring by the dynamic NMR studies.



1: ciguatoxin (CTX1B)

Our strategy for the construction of fused oxonene **2** is summarized in Scheme 1. We envisioned that the oxonane ring in **3** could be formed by SmI_2-promoted intramolecular Reformatsky reaction[7] of bistetrahydropyranyl ether **4**. Being matched with the need to attempt this cyclization, Martín and co-workers

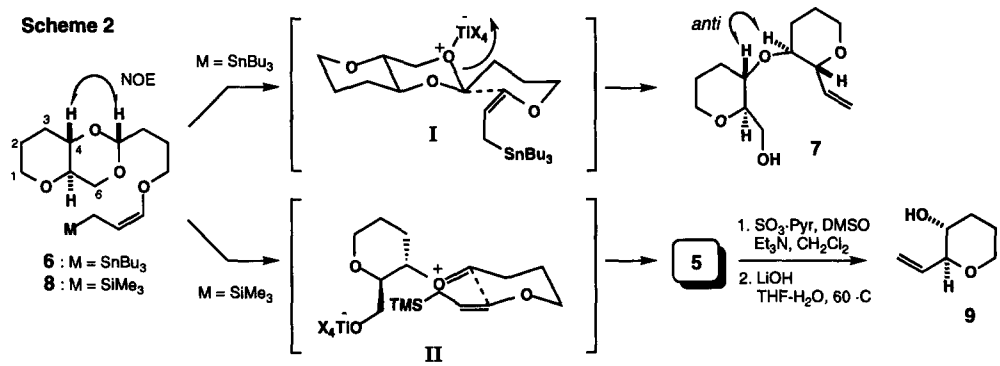
Scheme 1



2 **3** **4** **5**

recently reported the synthesis of optically active *O*-linked oxacycle **5**.[8] On the contrary to this report, however, treatment of γ-oxoallylstannane **6** with $TiCl_3(Oi\text{-}Pr)$ (CH_2Cl_2, -78 °C) led to undesired compound **7** with eventual *trans-anti-trans* stereochemistry[9] as the major product in 60% yield instead of the desired and reported *trans-syn-trans* ether **5** (Scheme 2). The stereochemical outcome of this cyclization can be rationalized by complexation of the Lewis acid to sterically the more accessible dioxane oxygen on C6 followed by direct S_N2 displacement by the allylstannane as shown in **I**.[10] On the other hand, upon treatment of less reactive γ-oxoallylsilane **8** with $TiCl_4$-PPh_3 (CH_2Cl_2, -78 to 0 °C),[11] the diastereoselectivity reversal was observed to furnish the desired **5** as the major product in 41% yield along with **7** (8%) and *cis* isomers (23%). Configurations of the stereogenic centers within the newly generated tetrahydropyran ring in **5** was unambiguously established by its retro-aldol cleavage to give *trans*-substituted **9**, the absolute configuration of which was determined by the modified Mosher's method.[12] Cyclization of the significantly less reactive γ-oxoallylsilane **8**, in comparison to the corresponding stannane **6**, would proceed in the S_N1 pathway[10] and thus the predominant formation of **5** from **8** may be explained by the less congested approach of the γ-oxoallylsilane to the oxocarbenium ion as shown in the transition structure **II**.

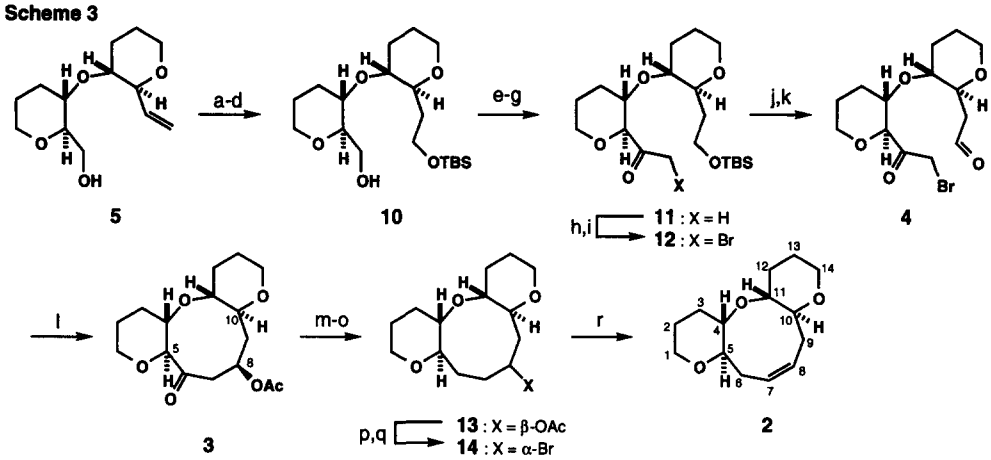
Scheme 2



Acetylation of **5**, hydroboration with 9-BBN followed by oxidation, protection of the resulting hydroxyl as its *t*-butyldimethylsilyl ether, and deacetylation in this sequence provided alcohol **10** (Scheme 3). The alcohol **10** was converted by standard methods to methyl ketone **11**, which was then transformed into α-bromo ketone **12** by trimethylsilyl enol ether formation and subsequent treatment with NBS. Removal of the silyl protecting group in **12** was followed by oxidation to provide aldehyde **4**.

The crucial SmI_2-promoted intramolecular Reformatsky reaction[7] of **4** proceeded smoothly to effect cyclization to an oxonane ring. Namely, treatment of **4** with five equivalents of SmI_2 in THF (10 mM) at -78 °C afforded a tricyclic compound, which was directly acetylated in one-pot with Ac_2O and DMAP to furnish β-acetoxy ketone **3** in 62% yield as a single stereoisomer.[13]

Scheme 3



Reagents and conditions: (a) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, rt; (b) 9-BBN, THF, rt, then H_2O_2, $NaHCO_3$, rt; (c) TBSCl, imidazole, DMF, rt; (d) DIBAL-H, CH_2Cl_2, -78 °C, 76% (four steps); (e) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C; (f) MeMgBr, THF, -78 °C, 87% (two steps); (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt, 69%; (h) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, -10 °C; (i) NBS, THF, 0 °C; (j) CSA, MeOH-CH_2Cl_2, 0 °C, 88% (three steps); (k) SO_3-pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C; (l) SmI_2, THF, -78 °C; then Ac_2O, DMAP, 0 °C, 62% (three steps); (m) $NaBH_4$, MeOH, 0 °C; (n) PhOCSCl, DMAP, CH_3CN, rt, 85% (two steps); (o) *n*-Bu_3SnH, AIBN (cat.), toluene, 80 °C, 78%; (p) DIBAL-H, CH_2Cl_2, -78 °C; (q) Ms_2O, *i*-Pr_2NEt, LiBr, CH_2Cl_2, 0 °C to rt; (r) KO*t*-Bu, DMSO, rt, 58% (three steps).

Completion of the synthesis required introduction of a *cis*-double bond on the oxonane ring in **3**. $NaBH_4$ reduction of the ketone in **3** and deoxygenation of the resultant hydroxyl provided acetate **13**. After deacetylation of **13**, treatment of the alcohol with Ms_2O and *i*-Pr_2NEt in the presence of LiBr gave the corresponding bromide **14**. Finally, exposure of **14** to KO*t*-Bu in DMSO led to a 5:1 mixture of the targeted oxonene **2** and its regioisomer (58% combined yield from **13**), which were easily separated by silica gel column chromatography.

As seen for ciguatoxin, the ^1H and ^{13}C NMR signals on the oxonene ring in **2** extremely broadened at room temperature. As the temperature decreased, these signals sharpened and separated as two sets of peaks, representing two alternating conformers. The population ratio of these conformers is nearly **A**:**B** = 1:1 in pyridine-d_5. The structures of these conformers were assigned by $^3J_{H,H}$ data[14] at low temperature as shown in Figure 1, and appeared to mimic the ring F of ciguatoxin closely except the ratio of two conformers. The free energy of activation for the conformational change was estimated to be approximately 14 kcal/mol from the coalescence temperature (28 °C).

The synthetic strategy described herein provides a possible solution to the construction of the oxonene ring region of ciguatoxins. Further synthetic studies toward ciguatoxins and their designed homologues are currently underway.

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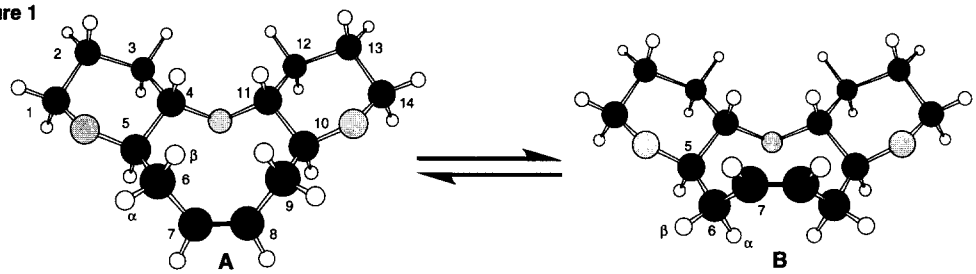
Figure 1



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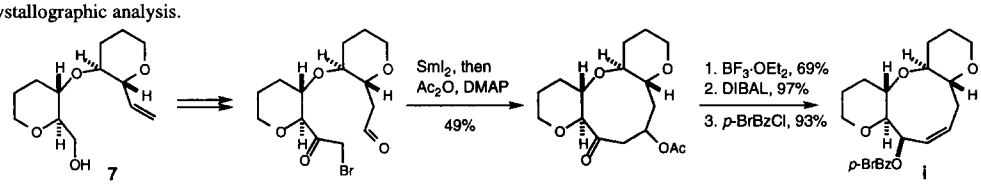
9. The *trans-anti-trans* arrangement of **7** was firmly established by converting it to *p*-bromobenzoate **i** and an X-ray crystallographic analysis.



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12. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096; presence of some impurities in **9** made its optical rotational value unreliable.
13. *Syn*-relationship between angular protons in **3** was confirmed by NOE experiments, by which the stereochemistry of the newly generated secondary hydroxyl at C8 was also assigned on the basis prominent NOEs due to H-5/H-8 and H-8/H-10.
14. Selected ^{1}H NMR data (C_5D_5N, -20 °C, 500 MHz) for conformers **A** and **B**. Major conformer **A**: δ 5.73 (m, 7-H), 3.04 (dd, $J_{5,4}$ = 9.5 Hz, $J_{5,6\beta}$ = 9.5 Hz, 5-H), 2.95 (ddd, $J_{6\beta,5}$ = 9.5 Hz, $J_{6\beta,6\alpha}$ = 12.5 Hz, $J_{6\beta,7}$ = 9.5 Hz, 6β-H), 2.30 (dd, $J_{6\alpha,6\beta}$ = 12.8 Hz, $J_{6\alpha,7}$ = 4.9 Hz, 6α-H). Minor conformer **B**: δ 6.00 (m, 7-H), 3.34 (5-H, overlapped), 3.07 (ddd, $J_{6\alpha,5}$ = 5.5 Hz, $J_{6\alpha,6\beta}$ = 14.0 Hz, $J_{6\alpha,7}$ = 9.8 Hz, 6α-H), 2.19 (dd, $J_{6\beta,6\alpha}$ = 14.0 Hz, $J_{6\beta,7}$ = 3.7 Hz, 6β-H).

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