

## Synthetic Study of Hemibrevetoxin B

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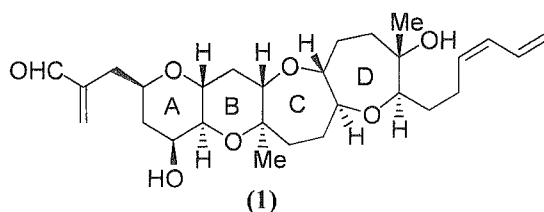
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## 論 文 内 容 要 旨

### CHAPTER - 1: Introduction

Along the Florida coast, the dinoflagellate *Gymnodinium breve* often form a blooms, leading to massive mortality of fish. Large blooms of this organism (red tides) can kill hundreds of tons of fish a day. The blooms sometimes cause human irritation of eyes and throat in the coastelarea<sup>1</sup>, and the contamination of shell fish, occasionally result in human poisoning cases. The toxic principle was identified as Brevetoxin B. Further efforts for isolation and structure elucidation of this family revealed many types of marine polycyclic ethers, which include brevetoxin A, hembrevetoxin B, gambieriol, gymnocin A, yessotoxin and so on.

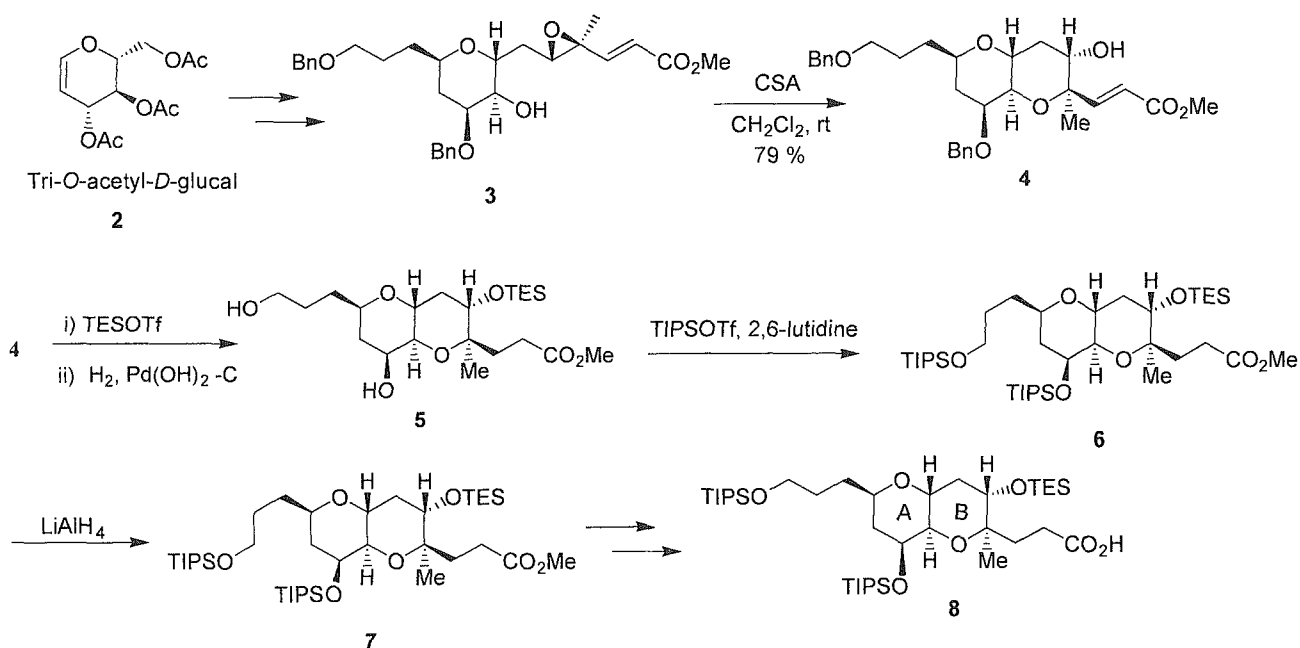
In 1989, Shimizu et al.<sup>2</sup> reported the isolation of a new type of marine polycyclic ether, Hemibrevetoxin **B (1)** from *Gymnodinium breve*, having about half of the molecular size of brevetoxins. The structure consists of a trans-fused six-, six-, seven-, seven-membered tetracyclic ether core (ABCD-ring) containing 10 chiral centres, an  $\alpha$ -vinyl moiety, and a (Z)-diene side chain. Since its isolation as the smallest member of marine polycyclic ethers, synthetic efforts by numerous organic chemists have been focused on.



## CHAPTER - 2 : Synthetic Study of Convergent Synthesis of Hemibrevetoxin B

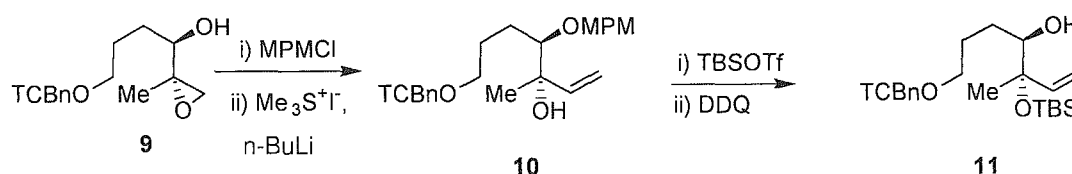
### 2-1. Synthesis of the AB ring segment

Synthesis of the AB ring segment **8** is illustrated below. The alcohol **3**, prepared from **2** by known procedure,<sup>3</sup> was converted to **4**. Then protection of the alcohol as TES ether followed by hydrogenation and simultaneous debenzoylation of **4** were performed by using  $H_2/Pd(OH)_2-C$  to give the diol **5**. The resulting diol was protected as TIPSO ether with TIPSOTf/ 2,6-lutidine to give **6**. The ester functionality of **6** was reduced to alcohol **7** by using  $LiAlH_4$ . The alcohol **7** was then subjected to stepwise oxidation using  $SO_3$  and  $NaClO_2$  to furnish the carboxylic acid **8**.



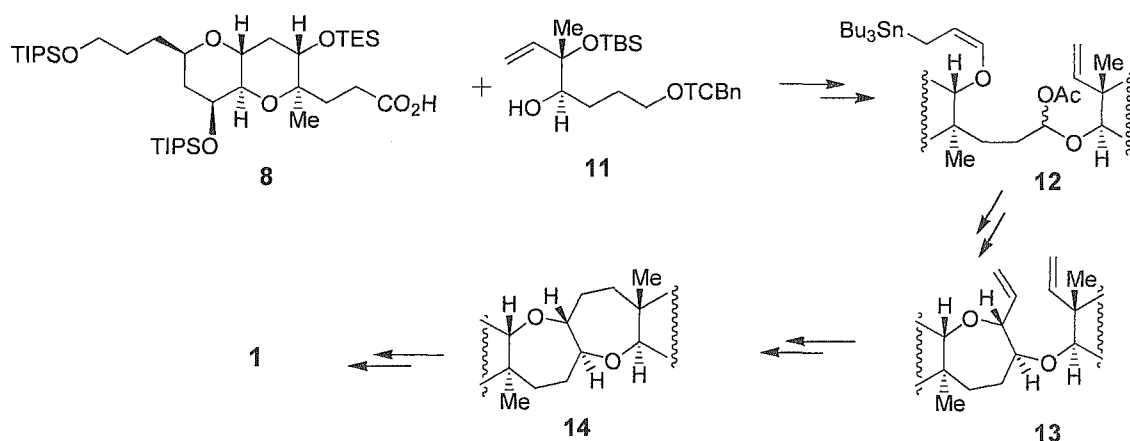
### 2-2. Construction of the D ring precursor

The D ring precursor **11** was prepared from the known epoxide **9**<sup>1</sup>. Protection of **9** with MPMCl/NaH and then treatment with dimethylsulfonium methylide generated in situ, afforded allylic alcohol **10** in 77% yield. Protection of the resulting tertiary alcohol with TBSOTf/ 2,6-lutidine followed by the MPM deprotection provided the alcohol **11** in 70% yield.



### 2-2. Connection of AB Ring Segment and D Ring Precursor

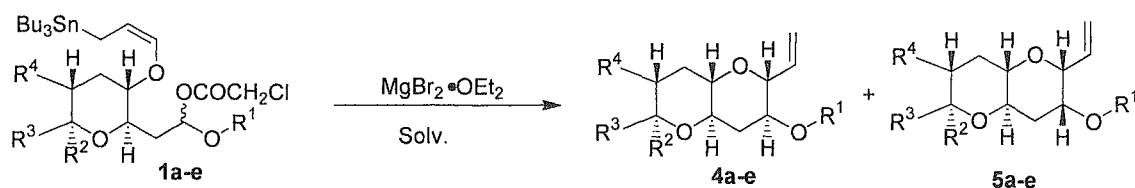
The cyclization precursor **12** has been prepared from the carboxylic acid **8** and the alcohol **11**. Next the convergent construction of the key intermediate **13** was achieved via the intramolecular allylation of  $\alpha$ -acetoxy ether **12** followed by ring closing metathesis. The polycyclic framework **14** was constructed from **13**, which was converted to **1** in our previous synthesis.<sup>3</sup>



### CHAPTER-3: Effect of molecular size on stereochemistry of cyclization of allyltin acetals

One of the latest stage in our convergent synthesis of naturally occurring polycyclic ether brevetoxin B<sup>5</sup> was the cyclization of the allyltin acetal **1a** leading to the formation of C-C bond (**Scheme 3-1**). The trans product **4a** was required for the construction of the target molecule. However, in the first try a 1:1 mixture of the trans- and cis-cyclization products **4a** and **5a** was obtained upon treatment of **1a** with MgBr<sub>2</sub>·OEt<sub>2</sub>. Nevertheless, by changing the solvent from dichloromethane to acetonitrile high trans-selectivity was achieved.

**Scheme 3-1**



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Yield, 4 : 5 (CH <sub>2</sub> Cl <sub>2</sub> )	Yield, 4 : 5 (CH <sub>3</sub> CN)
<b>1a-5a</b>		Me			78%, 50 : 50	82%, >95 : 5*
<b>1b-5b</b>		H	H	H	75%, 62 : 38	88%, >95 : 5*
<b>1c-5c</b>	(Me <sub>2</sub> CH) <sub>2</sub> CH	H	H	H	87%, 67 : 33	74%, 83 : 17
<b>1d-5d</b>	Me <sub>2</sub> CH	H	H	H	80%, 41 : 59	24%, 73 : 27
<b>1e-5e</b>	PhCH <sub>2</sub> CH <sub>2</sub>	H	H	H	82%, 53 : 47	78%, 77 : 33

\*Note: cis-isomer was detected only as a weak spot on TLC, but not in the NMR of a crude reaction mixture

Hence, the appropriate model compound for the detection of the solvent dependence of stereoselectivity must have at least two trans-fused six-membered rings imitating the structure of **1a**. Indeed, the compound **1b** gave exclusively *trans*-product **4b** after cyclization in acetonitrile (Scheme 1).

Thus, we have found that the marked solvent effect on the stereoselectivity of the cyclization observed for the reaction of polycyclic ether **1a** was hardly to be detected if one would try to optimize the reaction conditions using a small model compound like **1c-e**. On the other hand, reasonable model **1b** was constructed using the mechanistic computational analysis. It is interesting to realize that although the modern theory of nucleophilic substitution is elaborated far beyond the simple discrimination between  $S_N1$  and  $S_N2$  mechanisms,<sup>6</sup> we were still unable to find any clear precedents that could help to understand the experimentally observed solvent effect on the stereoselectivity. It might mean that a thorough mechanistic consideration is advisable in all important cases.

#### Chapter — 4 : Conclusion

1. A convergent formal total synthesis of hemibrevetoxin B (**1**) was achieved, via the intramolecular allylation of an  $\alpha$ -acetoxy ether and ring-closing metathesis. [ Chapter -2]
2. The origin of the marked solvent effect in the cyclization of the brevetoxin precursors was determined, where as in the small model compound the marked solvent dependence is absent. [ Chapter-3]

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## 論文審査の結果の要旨

海洋産の渦鞭毛藻が生産するポリ環状エーテルは、その特異な構造と強力な生理活性から多くの注目を集めている。しかし、天然からの入手がきわめて困難であるため、全合成による試料供給が重要な課題となっている。Touchy君は、当研究室で開発された手法を利用してヘミブレベトキシシンBの収束的形式全合成を行い、ポリ環状エーテル合成に関する本手法の一般性を確立した。また、本合成の鍵段階である分子内アリル化反応について、DFT計算を用いた遷移状態モデルの考察を行い、立体選択性に対する溶媒効果を明らかにした。

第一章では、ヘミブレベトキシシンBの収束的合成について検討した。この化合物は1989年に赤潮の原因プランクトンから単離されたポリ環状エーテルである。まず、トリアセチルグルカールを光学活性源とし、酸触媒によるエポシアルコールの分子内反応を用いることでAB環セグメントに相当するカルボン酸を合成した。D環前駆体となるアルコールセグメントは、シャープレスの不斉エポキシ化反応を用いることで光学活性体を合成した。得られた二つのセグメントを山口法によって連結した後、アリルスズ部分を導入、さらに改良リチノフスキー法によってアセチル基を導入した。得られた環化前駆体に対してルイス酸による分子内アリル化を行い、対応する環化体を収率良く得た。続いて閉環メタセシスを行った後、二重結合の還元と脱保護を行い、既知の合成中間体を得た。この化合物から天然物への変換は既に当研究室で報告しており、この段階でヘミブレベトキシシンBの形式全合成が達成された。

第二章では、ポリ環状エーテル合成の鍵反応である分子内アリル化について、立体選択性に及ぼす溶媒の効果についてDFT計算を用いて調査した。その結果、アセトニトリルを溶媒として用いた場合にはカルボカチオン中間体に溶媒が配位し、目的物を与える遷移状態を安定化していることがわかった。一方、塩化メチレン中の反応ではこのような安定化がみられず、立体選択性が低下することが予想された。これらの結果は実験事実と良く一致しており、今後反応を設計していく上で重要な知見である。

以上の成果は本人が自立して研究活動を行うに必要な高度の研究能力と学識を有していることを示している。よって、Abeda S. Touchy提出の論文は博士（理学）の学位論文として合格と認める。