論文内容の要旨

論文題目　Total Synthesis of (–)-Brevisin: A Concise Synthesis of a New Marine Polycyclic Ether for its Practical Supply

（(–)-ブレビシンの全合成：実践的供給を目指した
新規海産ポリ環状エーテルの効率的全合成）

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Abstruct

A polycyclic ether (–)-brevisin (**1**, Figure 1) was isolated from the red tide dinoflagellate *Karenia brevis*, which produces a variety of polycyclic ethers such as brevetoxins, brevenal, and a monocyclic ether amide brevisamide. Its unique structure consists of two fused tricyclic ether ring assemblies bridged by a methylene carbon and a conjugated aldehyde side chain, which is similar to brevenal and brevisamide. Interestingly, in spite of its unique skeletal structure which is divided into two tricyclic ether units by the methylene, **1** inhibits the binding of tritiated 42-dihydrobrevetoxin B (PbTx-3) to the voltage sensitive sodium channels (VSSC). However, similarly to the other marine polycyclic ethers, the biological activities have not been fully investigated due to the extremely small amount of supply from natural sources. In order to elucidate its interaction with VSSC and evaluate its other biological activities, chemical synthesis to supply material was essential.

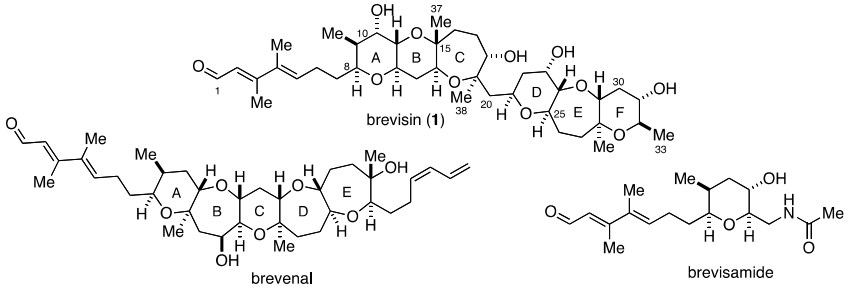


Figure 1.　Structures of brevisin (**1**), brevenal, and brevisamide

Synthesis of a BC/DE ring model of brevisin for diastereomeric confirmation through the acyclic junction

The separated skeletal structure in the center of the molecule is quite unusual among marine polycyclic ethers, and the methylene-linked structure is presumed to generate molecular flexibility, which plays an important role in an interaction with VSSC. In order to elucidate the interaction of **1** with VSSC, structural confirmation was essential. Firstly, the author synthesized a BC/DE ring model (**2**, Figure 2) for diastereomeric confirmation through the acyclic junction. The NMR chemical shifts from CH-14 to CH-25 of **2** were compared with those of **1**, as listed in Table 1. The observed chemical shifts of **2** around methylene junction agreed well with those of **1**, while relatively large difference in the B ring and the E ring regions are considered to be due to the absence of the A and the F rings. The synthetic BC/DE ring model bear a strong similarity to the same region of brevisin in its NMR data, supporting the diastereomeric relation of **1** around methylene juncture. The unique structure of brevisin was confirmed as depicted in **1** by the partial synthesis. Then, the author began the total synthesis of **1** based on this confirmation.

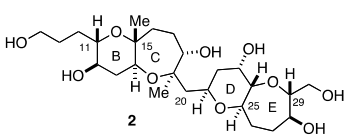


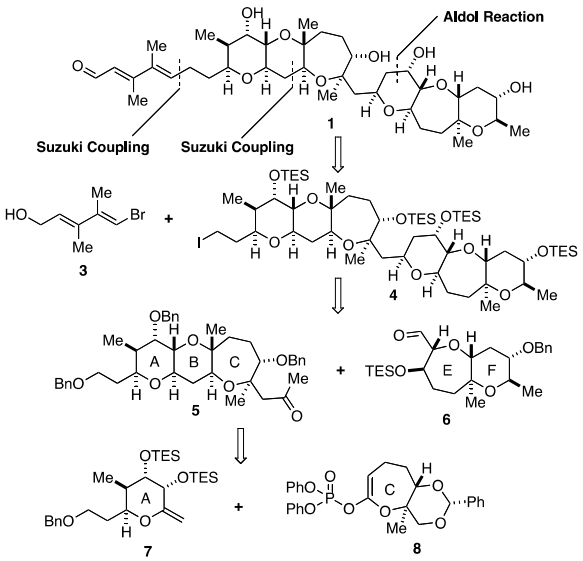
Figure 2. Sturucture of the BC/DE ring model (**2**)

Table 1. NMR chemical shifts of **1**, **2**, and their differences (Δδ) in pyridine-d_5

	^{1}H NMR			^{13}C NMR		
pos	**1**	**2**	Δδ	**1**	**2**	Δδ
14	4.40	4.42	–0.02	71.6	71.6	0.0
15	—	—	—	78.8	77.0	1.8
15-Me	1.50	1.54	–0.04	16.7	16.4	0.3
16a	2.69	2.70	–0.01	35.8	35.7	0.1
16b	1.75	1.75	0.00			
17a	2.06	2.05	0.01	26.8	26.7	0.1
17b	2.06	2.04	0.02			
18	4.47	4.45	0.02	73.5	73.2	0.3
19	—	—	—	81.1	80.9	0.2
19-Me	1.67	1.66	0.01	21.8	21.9	–0.1
20a	1.97	1.96	0.01	48.0	48.0	0.0
20b	1.75	1.72	0.03			
21	4.46	4.40	0.06	68.9	68.9	0.0
22ax	2.01	2.03	–0.02	40.8	41.1	–0.3
22eq	1.67	1.69	–0.02			
23	4.48	4.37	0.11	67.9	67.7	0.2
24	3.61	3.33	0.28	83.8	84.9	–1.1
25	4.10	4.03	0.07	74.8	75.4	–0.6

Synthetic plan

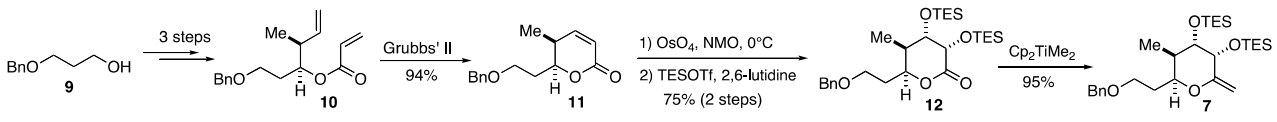
The employed synthetic plan is summarized in Scheme 1. Side chain fragment **3** and iodide fragment **4** would be connected by means of Suzuki–Miyaura cross coupling. Polycyclic ether core would be synthesized from the ABC ring methyl ketone **5** and the EF ring aldehyde **6** by aldol addition and subsequent construction of the D ring. The tricyclic ether **5** was synthesized from the A ring exocyclic enol ether **7** and the C ring ketene acetal phosphate **8** by a Suzuki–Miyaura cross coupling-based strategy invented in this laboratory.



Scheme 1. Synthetic plan

Synthetic of the ABC ring

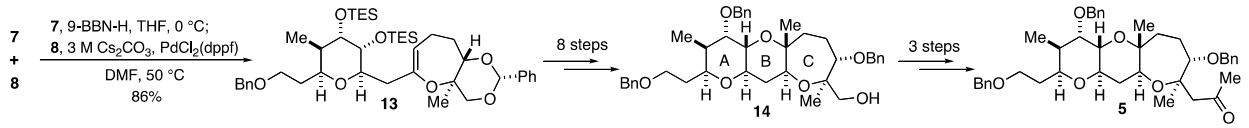
The synthesis of A ring fragment **7** started from 3-benzyloxy-1-propanol (**9**), which was converted to acrylate **10** in 3 steps. Ring-closing metathesis of **10** by Grubbs' second-generation catalyst furnished α,β-unsaturated lactone **11** in 94% yield. Dihydroxylation of **11** by OsO_4 followed by protection with TES groups gave lactone **12**. Treatment of **12** with Petasis reagent led to the A ring exocyclic enol ether **7** (Scheme 2).



Scheme 2. Synthesis of the A ring

The A ring fragment **7** was connected by Suzuki–Miyaura cross coupling to the C ring ketene acetal phosphate

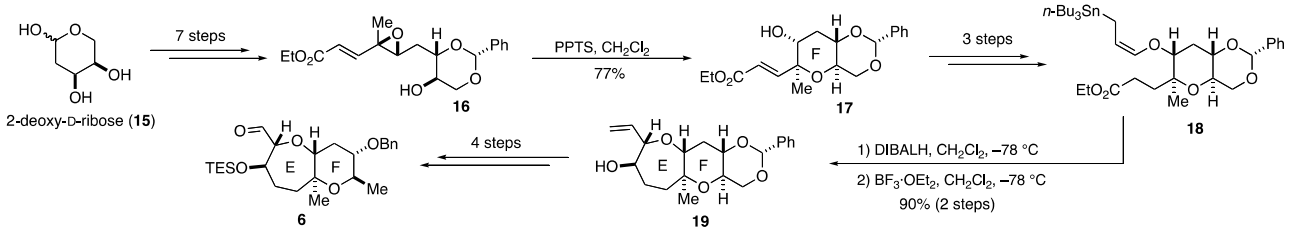
8, which was prepared in 8 steps from commercially available 2-deoxy-D-ribose. Cross-coupled product **13** was converted to tricycles **14** by the construction of the B ring. Then the ABC ring methyl ketone **5** was synthesized in 3 steps from alcohol **14** (Scheme 3).



Scheme 3. Synthesis of the ABC ring

Synthetic of the EF ring

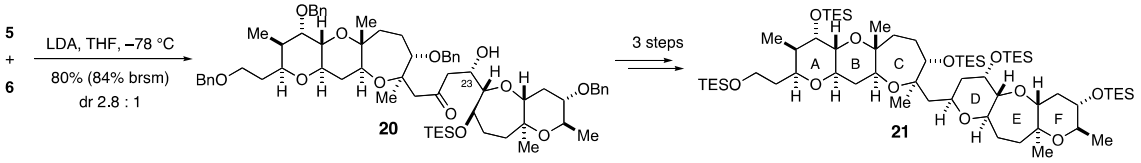
The synthesis of the EF ring fragment **6** started from acid catalyzed 6-*endo* cyclization of hydroxy epoxide **16** to afford pyran **17**. Pyran **17** was converted to allylstannane **18** in 3 steps. This ester **18** was reduced to the corresponding aldehyde by DIBALH, and then treated with $BF_3{\cdot}OEt_2$ to furnish the EF ring compound **19**. Then the EF ring aldehyde **6** was synthesized in 4 steps from **19** (Scheme 4).



Scheme 4. Synthesis of the EF ring

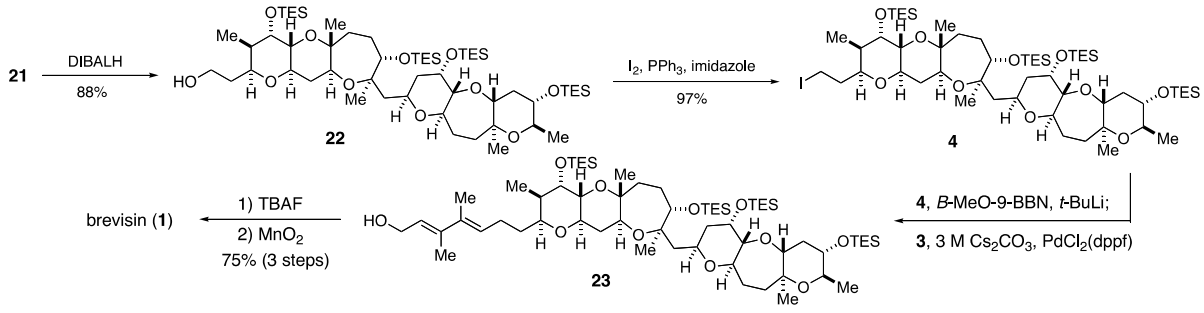
Total synthesis of (–)-brevisin

Connection of **5** and **6** by aldol addition is illustrated in Scheme 5. Treatment of the lithium enolate derived from **5** with aldehyde **6** furnished coupled product **20** as a separable mixture of C-23 diastereomers. Silyloxyketone **20** was converted to pentakis-TES ether **21** by construction of the D ring.



Scheme 5. Synthesis of the ABC/DEF ring polycyclic ether core

At this stage, in order to convert **21** to iodide **4**, only primary TES ether had to be selectively removed in the presence of four secondary TES ethers. During this work, the author established the highly selective deprotection of silyl ethers using DIBALH, and its application on pentakis-TES ether **21** gave primary alcohol **22** in 88% yield. The primary alcohol **22** was converted to iodide **4** with I_2, PPh_3, and imidazole. Finally, connection of the fragments **3** and **4** by means of Suzuki–Miyaura cross coupling followed by the deprotection of all silyl groups and chemoselective oxidation of the allylic alcohol gave rise to **1** in 75% yield for three steps. The optical rotation and the other spectroscopic data of synthetic **1** were identical with those of natural **1**.



Scheme 6. Completion of the total synthesis

In conclusion, the author accomplished the first total synthesis of (–)-brevisin (**1**). The polycyclic ether core was constructed in short steps by means of Suzuki–Miyaura cross coupling reaction and aldol addition as the key steps. It is noteworthy that the synthesis was accomplished in only 29 longest linear sequence from commercially available 2-deoxy-D-ribose. The present synthesis will be an important clue to elucidation of biological activities of marine polycyclic ether compounds.