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Total Synthesis and Structural Confirmation of Brevisamide, a New Marine Cyclic Ether Alkaloid from the Dinoflagellate *Karenia brevis*

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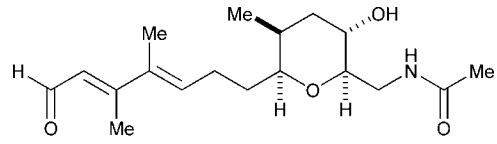
ABSTRACT



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The first total synthesis of brevisamide (1) has been accomplished in 21 linear steps starting from *cis*-but-2-ene-1,4-diol. A synthetic highlight is the Suzuki−Miyaura coupling between an ether ring fragment and a dienol side chain. This result confirmed the structure of 1 isolated from the dinoflagellate *Karenia brevis*.

Cyclic polyethers such as brevetoxins A and B, ciguatoxins, and maitotoxin are representative secondary metabolites produced by marine phytoplankton.[1] The dinoflagellate *Karenia brevis* is known to produce polycyclic ethers such as the brevetoxins and brevenal.[2−5] The brevetoxins cause massive kills of fish and marine animals such as dolphins and manatees along the Florida coast. The brevetoxins bind with high affinity to site 5 of the voltage-sensitive sodium channel (VSSC) in neurons, causing the channel to remain in the open state and inhibit channel inactivation, thus prolonging the duration of sodium currents across the membrane. The brevenals have an antagonistic activity against the brevetoxins.[6] In addition to these fascinating compounds, a cyclic ether alkaloid named brevisamide (**1**) was isolated from cultures of *K. brevis*.[7] Compound **1** consists only of a single tetrahydropyran ring furnished with a methyl and a hydroxyl substituents, a 3,4-dimethylhepta-2,4-dienal side chain, and an acetylated terminal amine. This ether amide is the first nitrogen-containing cyclic ether from *K. brevis* and can be regarded as a truncated analog of brevenal containing the A-ring portion and the dienal side chain. It has been suggested that **1** is assembled by a PKS/NRPS hybrid pathway in which glycine serves as a biosyn-

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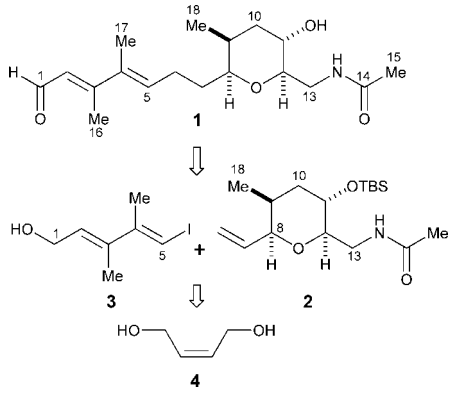
Scheme 1. Synthetic Strategy



thetic starter unit of **1** and hence may provide important biogenetic clues to the origin and biosynthetic assembly of polyethers in general.[8] The chemical synthesis of **1** is important to confirm the stereochemical details and at the same time supply additional material for biological testing. In this paper we report the total synthesis of **1** via Suzuki−Miyaura cross-coupling as a key reaction, which confirmed the stereochemical structure of the natural product.

The synthetic strategy employed was to build up both an amino cyclic ether fragment **2** and an iododienol unit **3** from a common starting material, *cis*-but-2-ene-1,4-diol **4**, and then couple these fragments by means of Suzuki−Miyaura coupling (Scheme 1).[9] In order to confirm the stereochemical features of the amino cyclic ether moiety in **1** as early as possible in the synthetic scheme, the ^{1}H and ^{13}C NMR chemical shifts of **11** were compared with those of **1** and found to be consistent with predicted ^{13}C values. Therefore, the acetylated amino group that was subject to a side reaction was introduced before the Suzuki−Miyaura coupling reaction. In our previous reports of polycyclic ether synthesis, Suzuki−Miyaura coupling has been used for stereocontrolled ether ring construction,[10] but the method was applied to extend the side chain from a terminal vinyl in this study.

Optically active homoallylic alcohol **5** was stereoselectively prepared following reported procedures (Scheme 2).[11] Diol **4** was protected with TBDPSCl and then oxidatively cleaved with O_3 to give the aldehyde. Generation of desired configuration for the hydroxyl and methyl groups in **5** was accomplished by Brown crotylation of this aldehyde. Thus addition of (+)-(*Z*)-crotyldiisopinocampheylborane gave the *syn*-homoallylic alcohol **5** as a single diastereomer (78%, 91% ee).[11] The *S* configuration at the hydroxyl-bearing methine group in **5** was confirmed by the modified Mosher method.[12] The homoallylic alcohol was again oxidized with O_3, followed by a Wittig reaction to generate the enoate in two steps. Hydrogenation and transesterification of the enoate yielded the lactone **6** in 71% after four steps.[13] The treatment of lactone **6** with KHMDS, DMPU, and Tf_2NPh at −78 °C gave ketene acetal triflate, which upon Stille coupling with CH_2═$CHSn$n$-Bu_3$ generated the dienol ether **7**. After hydroboration of **7**, the product was treated with H_2O_2 to furnish pyran **8** in 50% yield.[14] The relative configurations of **8** were confirmed by NOE correlations between H-8 and H-12, and Me-18 on C-9 and H-11, and by the large proton coupling constant of 9.2 Hz between H-11 and H-12.[15] Steric hindrance arising from the presence of the axial methyl group of **7** generated the desired stereoselectivity of hydroboration with thexylborane. Protection of the hydroxyl groups in **8** with TBSCl and subsequent selective deprotection of the TBS group on the primary alcohol gave a primary alcohol, which was oxidized to a carboxylic acid in **9** by treatment with TEMPO, NaOCl, and TBAC in 80% yield. Introduction of the terminal amino group was accomplished by means of Curtius rearrangement. The carboxylic acid **9** was treated with $(PhO)_2P(O)N_3$ (DPPA) and Et_3N in toluene at 80 °C for 4 h. The solvent was then replaced with THF, and treated with 4 N LiOH to generate the amine **10** in 85% yield.[16] The amino group was acetylated with acetic anhydride to afford amide **11**. At this point, NMR data were compared between **11** and the natural product **1** to reconfirm the stereochemical structure of **1** at the oxacyclic part. Although the ^{13}C chemical shifts around the amide region agreed well by comparison of the HSQC data, any slight differences in ^{1}H chemical shifts are attributable to the protective groups on the hydroxyl functions or the truncated side chain in **11**. Selective deprotection of the TBDPS group with TBAF and AcOH gave the desired primary alcohol. ^{1}H and ^{13}C NMR spectra of the alcohol were shown as **17** in Supporting Information. Oxidation of the alcohol in CH_2Cl_2−DMSO with SO_3•pyridine and Et_3N gave a crude aldehyde product, which without further purification was reacted with Ph_3P═CH_2 in a Wittig reaction to furnish the ether ring fragment **2**.

Unsaturated aldehyde **12** prepared from **4** in three steps[17] was treated with CBr_4, PPh_3, and Et_3N to give dibromoolefin **13**. Dehydrobromination with TBAF to give bromoacetylene **14** and subsequent debromination with *n*-BuLi at −78 °C

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(15) The carbon numbering corresponds to that of brevisamide (Scheme 1).

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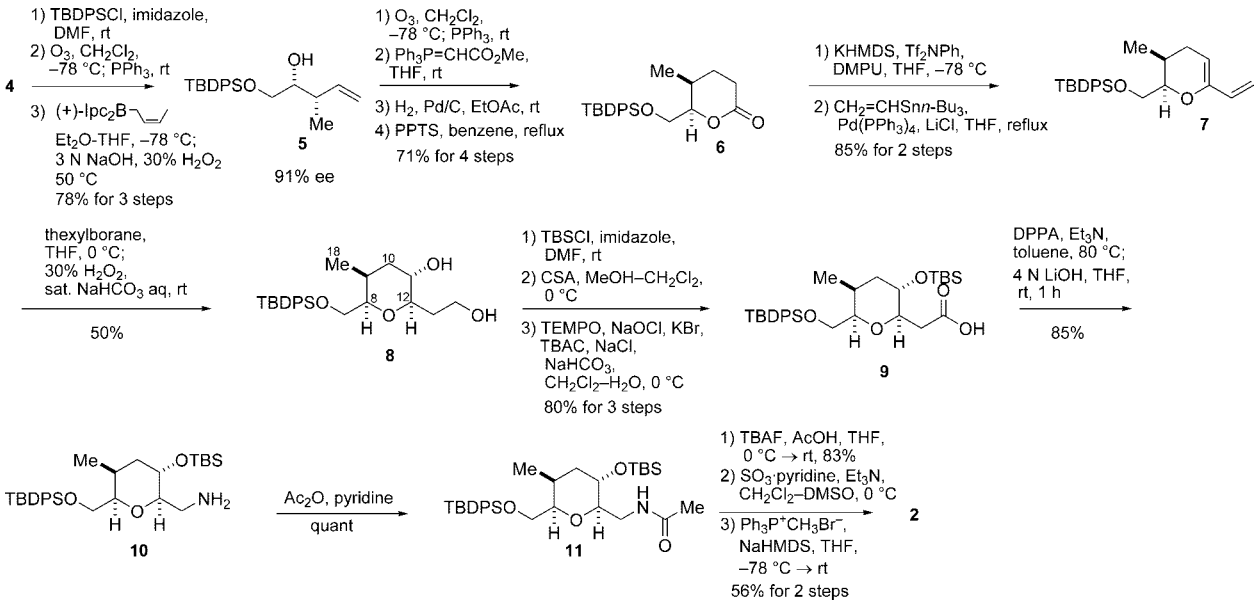
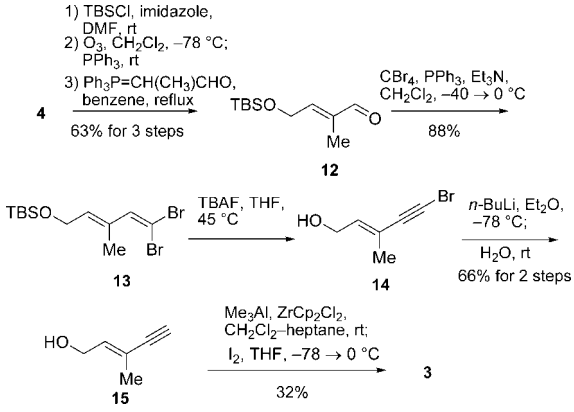
Scheme 2. Synthesis of Ether Ring Fragment **2**



afforded (2*E*)-3-methylpent-2-en-4-yn-1-ol **15**. Methylalumination-iodination of enynol **15** in the presence of $ZrCp_2Cl_2$ proceeded by *syn*-addition to afford the iododienol side chain fragment **3** with the desired *E*,*E* geometry (Scheme 3).[18]

Scheme 3. Synthesis of Iododienol Side Chain Fragment **3**



Connection of the key fragments **2** and **3** by Suzuki−Miyaura cross-coupling was accomplished in the following manner (Scheme 4). Hydroboration of **2** with 9-BBN produced alkylborane, which was reacted in situ with iododienol **3** in the presence of aqueous Cs_2CO_3 and a catalytic amount of $PdCl_2$(dppf), giving rise to a cross-coupled product. This crude product was treated with TBAF at 0 °C to give dienol **16** in 40% yield. Finally, chemoselective oxidation of the allylic alcohol at C-1 in **16** with MnO_2 led to synthetic **1** in 55% yield.

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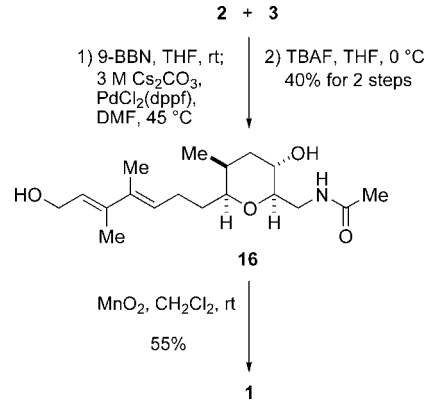
Scheme 4. Completion of Total Synthesis



^{1}H NMR spectra of synthetic **1** agreed with that of natural **1** and hence confirmed the structure of **1** including relative configurations. The magnitude of optical rotation of both natural and synthetic **1** was not quite identical probably because of the extremely small amount of natural **1** available but nevertheless showed the same negative rotation, and thus the absolute configuration of **1** is suggested as shown in Scheme 1. The absolute stereochemistry of **1** using MTPA esters will be confirmed after accumulation of more natural product.

In conclusion, we have accomplished the first total synthesis of brevisamide (**1**). The cyclic ether core was constructed in a stereocontrolled manner including chiral induction via organoborane, and the amino group was introduced by means of the Curtius rearrangement. Geometry-controlled synthesis of the left-hand multisubstituted dienal side chain was achieved by methylalumination−iodination

of an enynol substrate. Finally, both fragments were coupled by Suzuki−Miyaura cross-coupling.

Brevisamide can be an important molecule for our understanding of the biosynthesis of fused polyether ring systems in general by epoxide-opening pathways. Future goals are to synthesize plausible biosynthetic intermediates of brevisamide to explore the epoxide-opening mechanism further.

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Supporting Information Available: General experimental procedures and characterization of all new compounds, **2**, **3**, MTPA esters of **5**, **6**−**11**, **13**−**14**, and **16**−**17**, and copies of NMR spectra for synthetic and natural **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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