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Synthesis of a proposed biosynthetic intermediate of a marine cyclic ether brevisamide for study on biosynthesis of marine ladder-frame polyethers

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ABSTRACT

A monocyclic ether alkaloid, brevisamide (**1**) was isolated from the dinoflagellate *Karenia brevis* that produces a variety of ladder-frame polyethers. Its proposed biosynthetic intermediate (**2**) comprising a linear backbone with an *E*-olefin functionality was synthesized for biosynthetic studies on the marine ladder-frame polyethers.

The red tide dinoflagellate *Karenia brevis*, is known to produce ladder-frame polyethers, brevetoxins[1–3] and brevenal.[4] Recently a monocyclic ether amide, brevisamide (**1**)[5] and a polycyclic ether, brevisin[6] were isolated from *K. brevis*. The brevetoxins and brevenal are characterized by ladder-frame polyether skeletons, while **1** consists of a single tetrahydropyran ring with a 3,4-dimethylhepta-2,4-dienal side chain and an acetylated terminal amine. Our recent success of chemical synthesis of **1** confirmed its unique structure.[7] Recently, synthetic works were accomplished by independent groups.[8–10] This cyclic ether amide is the first nitrogen-containing cyclic ether from *K. brevis* and can be regarded as a truncated analog of brevenal and brevisin containing the A-ring portion and the dienal side chain (Fig. 1). In comparison to progress in the structural elucidation and chemical synthesis of ladder-frame polyethers,[11,12] much less is understood about their biosynthesis specifically the formation of the fused or ladder-frame polyether ring systems. One particularly appealing hypothesis on the formation of these ladder-frame structures was put forward by Nakanishi which involves formation of ether rings by a stepwise or cascading series of condensations starting from a putative polyepoxide intermediate.[13] An intriguing new development in the assembly of ladder-frame polyethers was heralded by the recent report that polyether ladders form spontaneously from a suitable polyepoxide intermediate in polar solvent, but only if a template or nucleating hydroxytetrahydropyranyl functionality is built in to the intermediate.[14] This suggests the feasibility of a model in which only the first ether ring formed requires catalysis by an enzyme and that the remaining cyclizations proceed spontaneously governed by the spacing and configuration of the epoxide functionality. Consequently, brevisamide is an important molecule for our general understanding of the biosynthesis of fused polyether ring systems by epoxide-opening pathways.[5] Although the *E*-olefin **2** and epoxide **3** are plausible biosynthetic intermediates in the biosynthesis of **1** (Scheme 1), neither of these proposed linear intermediates have as yet been isolated from the dinoflagellate. While remarkable progress has been made in our understanding of the biosynthesis polyether antibiotics from actinomycetes at the molecular level, the biosynthetic genes of dinoflagellate polycyclic ethers have not been identified fully.[15,16] In order to obtain clues about this intriguing biosynthetic route, we undertook the synthesis of **2** with two goals in mind. First, it would serve as an HPLC

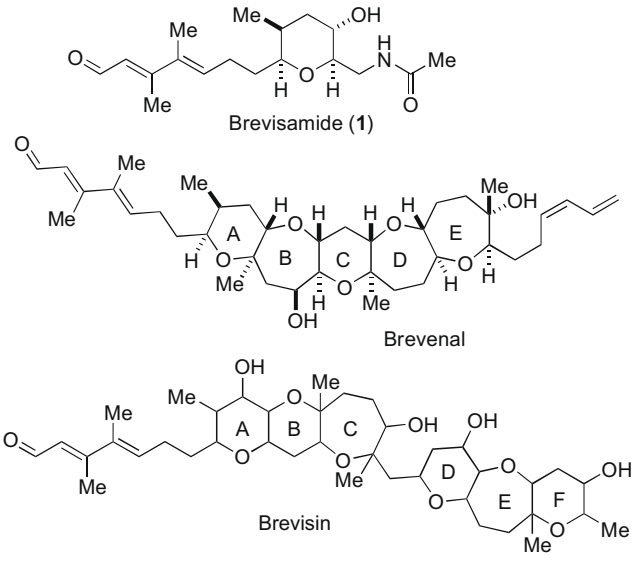

Figure 1. Structures of brevisamide (**1**), brevenal, and brevisin.

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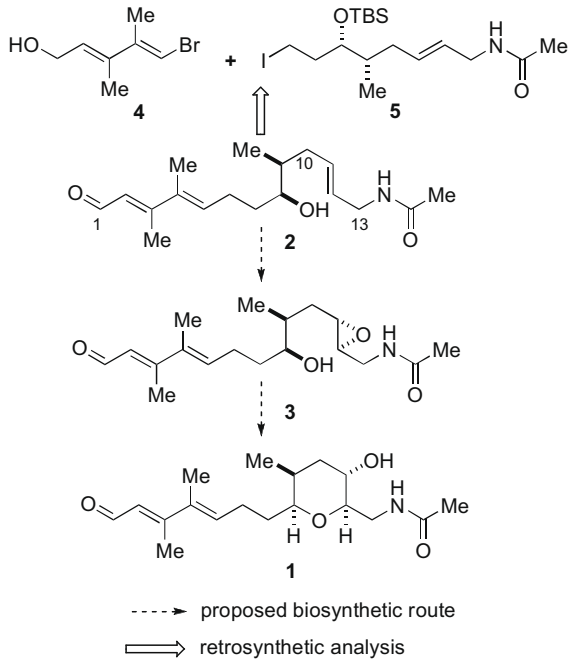
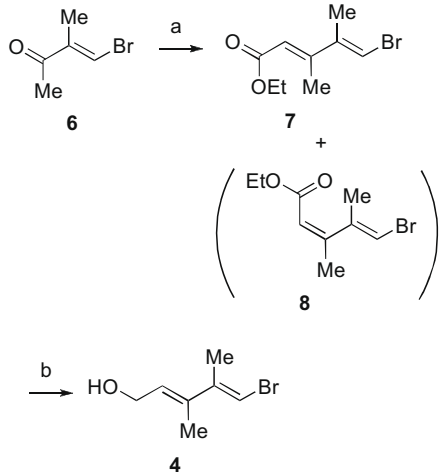


Scheme 1. Retrosynthetic analysis of **2** and proposed biosynthetic route of **1**.

standard material to assist in the search for biosynthetic precursors produced by cultures of K. brevis, and second it could serve as a substrate for epoxidation and subsequent cyclization enzymes present in the dinoflagellates. In this Letter we report chemical synthesis of the *E*-olefin intermediate **2** using a Suzuki–Miyaura cross coupling reaction.[17–19]

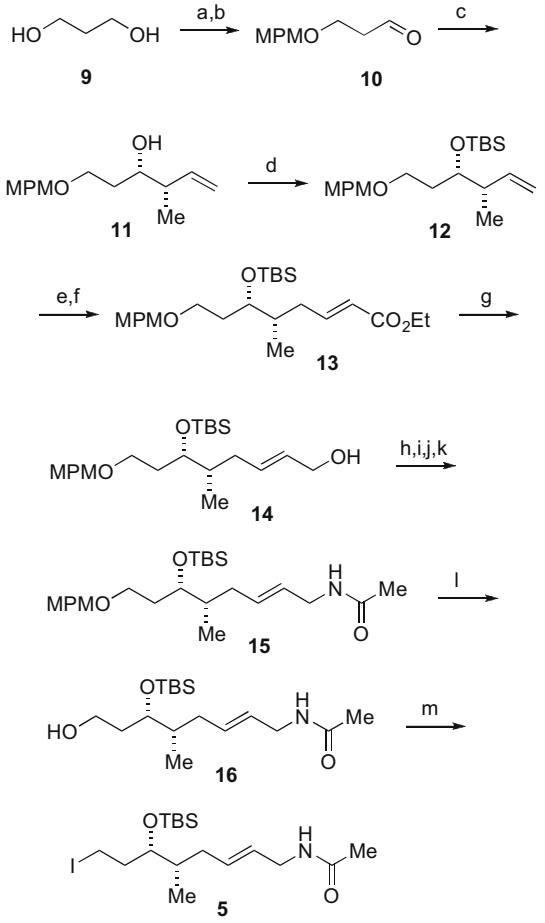
Our synthetic strategy using Suzuki–Miyaura cross coupling as a key reaction is shown in Scheme 1. The olefin intermediate **2** was synthesized by coupling between a dienol side chain fragment **4** and an iodoenamide fragment **5**. In our first total synthetic approach to **1** which was reported previously,[7] the iododienol side chain fragment and an ether ring exo-vinyl were joined via a Suzuki–Miyaura cross coupling.[7] However, the yield and reproducibility of the iododienol fragment which was prepared from *cis*-but-2-ene-1,4-diol were low, and therefore we synthesized a bromodienol fragment as a coupling material.

In this approach, the dienol fragment **4** was prepared from a reported bromoenone **6** (Scheme 2).[20] Horner–Wadsworth–Emmons reaction of **6** with $(EtO)_2P(O)CH_2CO_2Et$ in the presence of NaHMDS gave (*E*,*E*)-bromodienoate **7** and undesired (*Z*,*E*)-bromodienoate **8** in a highly stereoselective fashion (6:1). Reduction of the desired (*E*,*E*)-dienoate **7** with DIBAL afforded the dienol side chain fragment **4** in 98% yield.

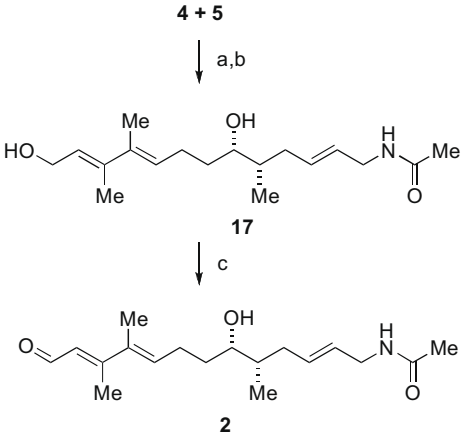


Scheme 2. Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, toluene, 0 °C to rt, 60% for **7**, 10% for **8**; (b) DIBAL, CH_2Cl_2, −78 °C, 98%.

Optically active homoallylic alcohol **11** was prepared stereoselectively following published procedures.[21] First aldehyde **10** was prepared in two steps from propane-1,3-diol **9**. Reagent-controlled enantioselective crotylation of aldehyde **10** using (*Z*)-2-butene and (+)-β-methoxydiisopinocampheylborane gave the desired (3*S*,4*S*)-alcohol **11** (46%). The absolute configuration of the hydroxy-bearing carbon of **11** was determined by a modified Mosher method.[22] Protection of the secondary alcohol with TBSCl gave TBS ether **12**. Hydroboration with 9-BBN–H followed by oxidative work-up, oxidation with TEMPO and $PhI(OAc)_2$, followed one-pot Wittig reaction with Ph_3PCHCO_2Et afforded enoate **13** in 69% yield for three steps from **11**. The enoate **13** was reduced with DIBAL to give allylic alcohol **14** in 98% yield. The alcohol **14** was converted to the iodide using imidazole, PPh_3, and I_2 which was converted to the azide with NaN_3 and then reduced to afford the amine. This amine was acetylated with acetic anhydride to give amide **15** in 83% yield over four steps. Removal of the MPM group with DDQ in phosphate buffer/CH_2Cl_2 generated alcohol **16** which was converted to iodide **5** with imidazole, PPh_3, and I_2 in 74% yield for two steps (Scheme 3).



Scheme 3. Reagents and conditions: (a) MPMCl, NaH, TBAI, THF, 0 °C to rt, 64%; (b) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, 0 °C, 94%; (c) (+)-(*Z*)-crotyldiisopinocampheylborane, Et_2O, THF, −78 °C; then 3 N NaOH, H_2O_2, reflux, 76%, 88% ee; (d) TBSCl, imidazole, DMF, 78%; (e) 9-BBN–H, THF; then $NaHCO_3$ aq, H_2O_2; (f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2; then $Ph_3P{=}CHCO_2Et$, 88% (two steps); (g) DIBAL, CH_2Cl_2, −78 °C, 98%; (h) I_2, PPh_3, imidazole, toluene; (i) NaN_3, DMF; (j) PPh_3, THF; then H_2O, 45 °C; (k) Ac_2O, pyridine, 83% (four steps); (l) DDQ, CH_2Cl_2, pH 7 phosphate buffer, 0 °C, 91%; (m) I_2, PPh_3, imidazole, toluene, 82%.



Scheme 4. Reagents and conditions: (a) **5**, *B*-OMe-9-BBN, *t*-BuLi, Et_2O, THF, −78 °C to rt; then **4**, 3 M Cs_2CO_3, $Pd(PPh_3)_4$, DMF; (b) TBAF, THF, reflux, 31% (two steps); (c) MnO_2, CH_2Cl_2, 0 °C, 98%.

Connection of the dienol side chain fragment **4** and the amide fragment **5** was accomplished by Suzuki–Miyaura cross coupling (Scheme 4). Treatment of **5** with *t*-BuLi and *B*-OMe-9-BBN produced a borate intermediate which was reacted in situ with bromodienol **4** in the presence of aqueous Cs_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$ to give rise the cross-coupled product.[23] The crude product was treated with TBAF under a reflux condition to give dienol **17**. Finally, chemoselective oxidation of the allylic alcohol at C-1 with MnO_2 led to the putative biosynthetic olefin precursor **2** in 30% yield for three steps.[24,25]

The revised synthesis of the dienol fragment for the coupling reaction led to a more efficient synthesis of the proposed biosynthetic intermediate **2**. Biosynthetic precursors such as the *E*-olefin and the epoxide intermediate have not been isolated from the dinoflagellate *K. brevis*, perhaps suggesting that conversion of such putative precursors as the *E*-olefin or epoxide to brevisamide proceeds spontaneously. Future studies to explore the biosynthesis of marine ladder-frame polyethers will be directed toward the epoxidation step and subsequent ring-opening enzymes in dinoflagellates using the intermediate **2**.

Acknowledgments

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23. To a solution of the iodide **5** (260 mg, 0.592 mmol) in anhydrous Et_2O (5 mL) at room temperature was added *B*-OMe-9-BBN (1.0 M solution in hexane, 1.8 mL, 1.8 mmol). After cooling to −78 °C, *t*-BuLi (1.58 M solution in pentane, 0.94 mL, 1.48 mmol) was added rapidly, followed by THF (5 mL). Then the reaction mixture was stirred at −78 °C for 10 min and allowed to warm to room temperature for 2 h. To the mixture were added 3 M aqueous Cs_2CO_3 (1.5 mL), the solution of the bromodienol **4** (206 mg, 1.08 mmol) in DMF (5 mL), and $Pd(PPh_3)_4$ (34.2 mg, 0.0296 mmol). After stirring for 16 h, usual work-up gave the crude cross-coupled product.
24. Data for **2**: $[\alpha]_D^{27}$ −14.3 (*c* 0.12, CH_3OH); IR (film) 3299, 2929, 1657, 1442, 1375, 1283, 1252, 1153, 1046, 970, 843, 750 cm^{-1}; ^{1}HNMR (500 MHz, CD_3OD) δ 10.10 (d, *J* = 8.0 Hz, 1H), 6.26 (dd, *J* = 7.0, 7.0 Hz, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.61 (ddd, *J* = 15.1, 7.5, 7.5 Hz, 1H), 5.47 (dt, *J* = 15.1, 5.9 Hz, 1H), 3.72 (d, *J* = 5.9 Hz, 2H), 3.48 (m, 1H), 2.41 (m, 1H), 2.34 (s, 3H), 2.30 (m, 1H), 2.21 (m, 1H), 1.93 (s, 3H), 1.93–1.87 (m, 1H), 1.88 (s, 3H), 1.56 (m, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}CNMR (100 MHz, CD_3OD) δ 194.4, 172.9, 161.0, 137.0, 132.7, 128.3, 126.2, 74.7, 42.3, 40.0, 37.4, 34.7, 27.2, 22.5, 14.5, 14.1, 14.0; HRMS (FAB) calcd for $C_{18}H_{29}O_3NNa$ [$(M+Na)^+$] 330.2045, found 330.2059.
25. A negative referee pointed out that **2** had not been isolated from the dinoflagellates. However, we think that **2** is a key compound to verify the proposed biosynthetic route of marine ladder-frame polyethers by using as a substrate for exploration of epoxidation and epoxide opening enzymes in the dinoflagellates. Therefore the synthesis of **2** is important and will accelerate biosynthetic studies on marine ladder-frame polyethers.