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Total Synthesis of Brevisamide

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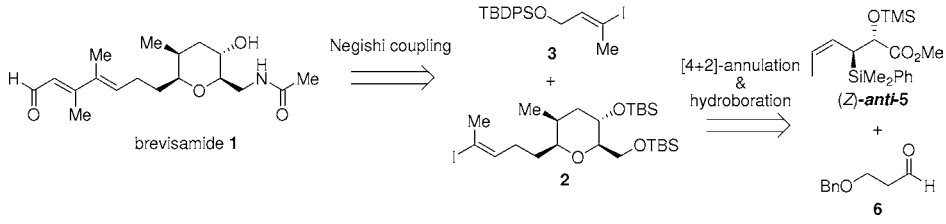
ABSTRACT



A convergent synthesis of brevisamide (1) is described based on the application of the crotyl silane-based [4 + 2]-annulation used for the preparation of the advanced oxygenated tetrahydropyran intermediate 2. The side chain bearing a conjugated (*E*,*E*)-diene was efficiently constructed under modified Negishi cross-coupling conditions.

A family of polycyclic ether toxins produced by red tide Dinoflagellate *Karenia brevis* have attracted significant interest due to their toxicity and structural complexity. For instance, the brevetoxins are known to exhibit potent neurotoxicity, which causes open state of voltage-sensitive sodium channel (VSSC) and disturbs inactivation, and brevenal exhibits antagonism against toxic effects caused by brevetoxins.[1] These toxins isolated from *K. brevis* have been attractive targets for synthetic chemists due to their unique structures, cyclic polyether core, and biological activities.[2]

Brevisamide[3] (**1**) was recently isolated by Wright's group (Center for Marine Science at University of North Carolina) while conducting experiments aimed at the identification of new metabolites from *K. brevis.* The structure elucidation, as well as the assignment of both relative and absolute stereochemistry of brevisamide (**1**), were initially established by 1D and 2D NMR studies and later confirmed by total synthesis.[4] A second total synthesis has recently appeard from Lindsley's laboratory.[5] Structural features of brevisamide (**1**) include an oxygenated tetrahydropyran core and a trisubstituted (*E*,*E*)-diene as a challenging component of the side chain (Figure 1). Additionally, brevisamide is the only metabolite of *K. brevis* that contains an amide. Since the biological properties of this molecule have not been disclosed, developing efficient synthetic strategies for this natural product will provide sufficient amounts to facilitate further biological evaluation.

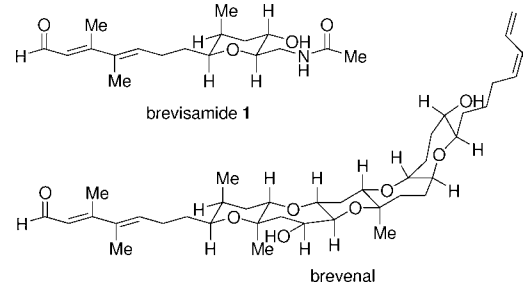


Figure 1. Structures of brevisamide (**1**) and brevenal.

Our synthetic plan intended to utilize a palladium-catalyzed Negishi cross-coupling to construct the conjugated (*E*,*E*)-

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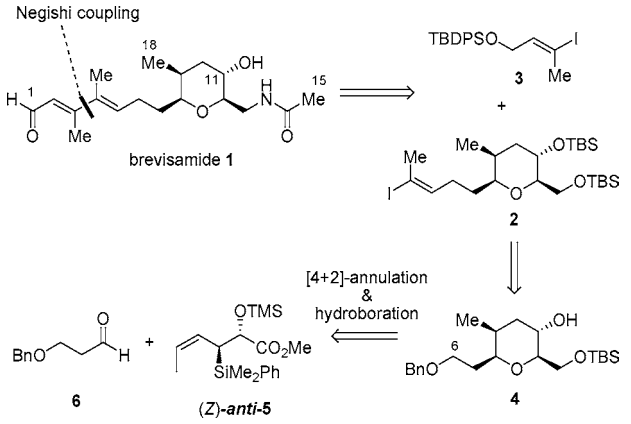
diene of brevisamide **1**. In this regard, we initially planed to disconnect C3−C4, which led to two fragments **2** and **3** (Scheme 1). Iodoalkene **3** will be an immediate precursor to

Scheme 1. Retrosynthetic Analysis of Brevisamide (**1**)



an alkenylzinc reagent generated in situ through lithium-haolgen exchange and transmetalation.[6] The hydroxyl-bearing center with an (*S*)-configuration at C11 will be introduced by diastereoselective hydroboration of an intermediate dihydropyran.[7] Further, the (*E*)-vinyl iodide in the side chain of fragment **2** will be installed though S_N2-type propynyl substitution at C6 and subsequent regioselective hydrozirconation followed by trapping with iodine.[8] The trisubstituted dihydropyran precursor to fragment **4** with a *cis*−*cis* relationship will be prepared through a [4 + 2]-annulation between (*Z*)-crotylsilane **5** and aldehyde **6**.[9]

The stereochemical outcome of the annulation products can be attributed to the configuration of the silane reagents as illustrated in Figure 2. In the case of a [4 + 2]-annulation with a (*E*)-crotylsilane,[9a] a 5,6-*trans*-dihydropyran is always favored. Stereochemical relationships between the 2- and

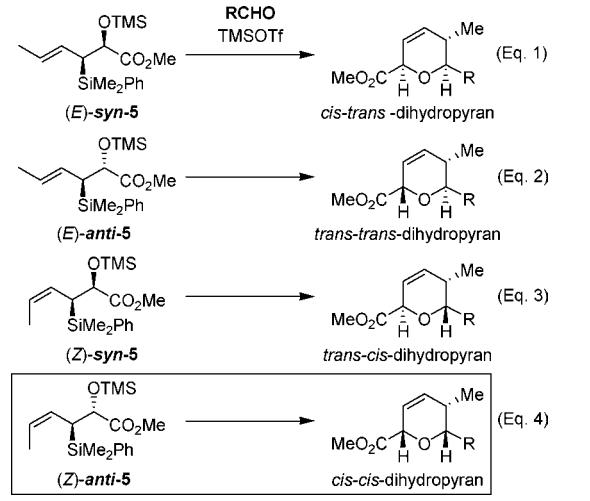
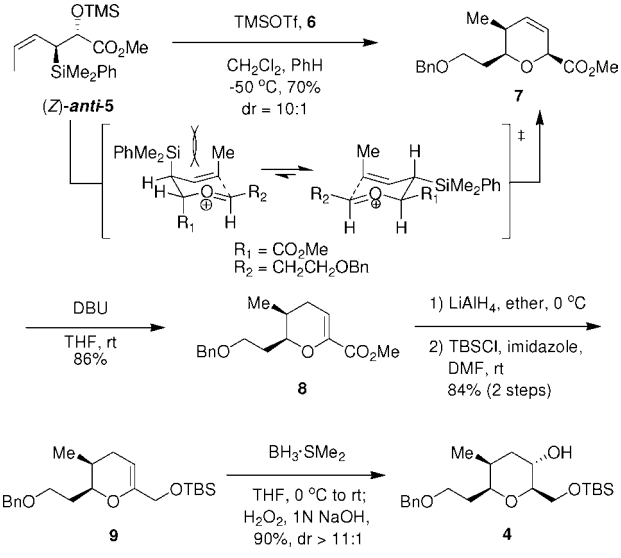


Figure 2. Stereochemical course of [4 + 2]-annulation of (*E*)- and (*Z*)-crotylsilane reagents.

6-substituents of dihydropyran are dictated by *syn*- and *anti*-relationship of crotylsilane. Therefore, *syn*- and *anti*-(*E*)-crotylsilane give 2,6-*cis*- and 2,6-*trans*-dihydropyran, respectively (Figure 2, eqs 1 and 2). In contrast, annulation of (*Z*)-crotylsilane selectively affords 5,6-*cis*-dihydropyran.[9b] In addition, 2,3-*syn*- and 2,3-*anti*-realtionships of (*Z*)-crotylsilane provide 2,6-*trans*- and 2,6-*cis*-dihydropyran, respectively (Figure 2, eqs 3 and 4), which is the opposite and complementary stereochemical outcome to that of (*E*)-crotylsilanes.

The synthesis of oxygenated tetrahydropyran fragment **2** was initiated with [4 + 2]-annulation of known (*Z*)-crotylsilane **5**[9b,10] with aldehyde **6** (Scheme 2), which afforded 5,6-*cis*-trisubstituted dihydropyran **7** in 70% isolated yield (dr = 10:1). In our initial plan, we desired diastereo-

Scheme 2. Synthesis of Hydroxytetrahydropyran Fragment **4**



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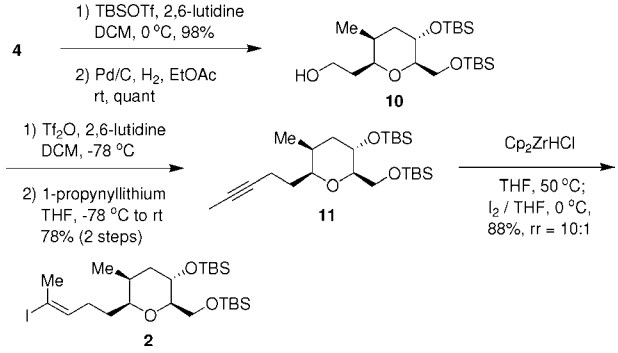
selective hydroboration of dihydropyran **7** to directly introduce the β-hydroxyl group at C11. Since hydroboration in a *trans,trans* dihydropyran system has been previously studied in our group,[7c,d] we applied the conditions that were used in previous examples (2.0 M BH_3·SMe_2 in THF) to the hydroboration of *cis,cis* dihydropyran **7**. However, hydroboration of **7** was found to be problematic, which gave the desired product in 40% yield (dr = 2.5:1) with varying amounts of degradation of **7**. Other experiments utilizing catecholborane in the presence of Wilkinson's catalyst or 9-BBN[7a,b] also proved to be unsuccessful.

At this point, we concluded that *cis,cis* dihydropyran **7** was not conformationally suitable for the desired stereochemical course of hydroboration. Therefore, we removed the chiral center at C12 by isomerization of the olefin into conjugation with the methyl ester in the presence of DBU,[11] after which that stereocenter could be regenerated through hydroboration of the allylic TBS ether. Then, LAH reduction of methyl ester and subsequent protection of the resulting allylic alcohol as a TBS ether gave a new hydroboration precursor **9**. Subsequently, hydroboration using BH_3·SMe_2 at 0 °C afforded the desired oxygenated tetrahydropyran **4** both in high yield and diastereoselectivity (90%, dr >11:1).

With useful quantities of secondary alcohol **4** in hand, we turned our attention to extending the left-hand side chain. Intermediate alcohol **4** was protected as its TBS ether, and hydrogenolysis of benzyl ether in ethyl acetate afforded primary alcohol **10** in high yield (Scheme 3). To install three

Scheme 3. Synthesis of the Fragment **2**



additional carbons at C6, S_N2-type alkyne substitution[12] was employed. Triflation of primary alcohol **10** using Tf_2O gave an unstable intermediate triflate ester that was used without purification. As such, this material was treated with 1-propynyllithium that was generated in situ by treatment of a propyne solution in THF with *n*-BuLi at −78 °C to afford alkyne **11**. However, this reaction turned out to be sensitive to the number of equivalents of nucleophile and cosolvent. For instance, 1.5 equiv of propynyllitihium gave only decomposition of triflate ester after 12 h. Using THF/HMPA (10:1) mixed solvent system gave the desired product **11** in 60% yield within 30 min, but this result was not reproducible when scaled up. An optimal condition was found when the triflate ester was treated with 5 equiv of propynyllithium in THF for 3 h, affording **11** in 78% (two steps).

Regioselective hydrozirconation of the internal alkyne **11** utilizing 2 equiv of Schwartz reagent in THF, followed by trapping of the organozirconium intermediate with I_2 successfully furnished the coupling precursor (*E*)-iodoalkene **2** in 88% yield (*E*/*Z* = 10:1).[8] Alternatively, silylcupration (5 equiv of CuCN, 10 equiv of $PhMe_2SiLi$) gave the desired vinyl iodide **2** with much lower regioselectivity (*E*/*Z* = ∼2:1).[2f,13]

The final stage of the synthesis required introduction of the aldehyde side chain with the assembly of the conjugated (*E*,*E*)-diene, which began with fragment coupling between different (*E*)-vinyl iodide fragments **2** and **3** under modified Negishi coupling conditions.[5] Although it has been reported that formation of this type of trisubstituted (*E*,*E*)-diene can be achieved using Stille coupling conditions, the use of silyl-protected vinyl stannane version of intermediate **3** afforded the contaminated diene with its homocoupling product.[2f] Treatment of vinyl iodide **3**[14] with an excess amount of *t*-BuLi and transmetalation of the resulting lithium anion with anhydrous $ZnCl_2$ generated an intermediate vinlyzinc species. Coupling of the in situ prepared zinc intermediate with the vinyl iodide **2** in the presence of 10 mol % of $Pd(PPh_3)_4$ provided a crude diene that was used without purification. The selective cleavage[15] of primary TBS ether using CSA afforded, after purification on silica gel, the pure (*E*,*E*)-diene **12** in 58% as a single regioisomer.

To install an acetyl amide in the right-hand side chain, the resulting primary alcohol was activated and substituted with azide using diphenylphosphoryl azide (DPPA) under Mitsunobu conditions.[16] Reduction of the azide[17] in the presence of NH_4OH followed by acetylation of the primary amine gave the acetyl amide **13** in 83% yield (two steps).

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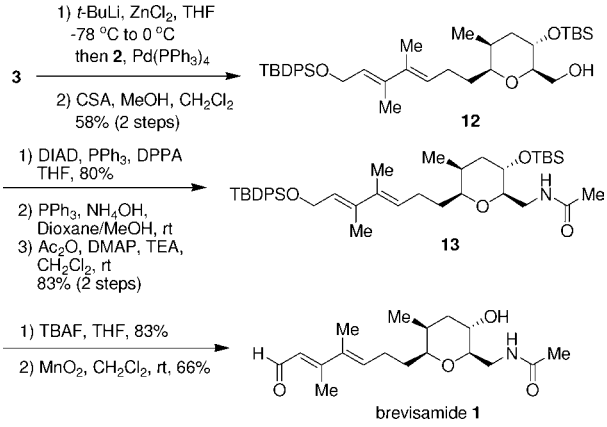
Deprotection of the two silyl ethers using TBAF gave an advanced diol intermediate, and chemoselective oxidation of the primary allylic alcohol in the presence of the secondary alcohol using excess amount of MnO_2 successfully afforded brevisamide **1** (Scheme 4).[2f,4,18]

Scheme 4. Completion of the Synthesis



In summary, the total synthesis of the brevisamide has been achieved in 17 steps with a 6.4% overall yield starting from *trans*-(Z)-crotylsilane **5**. The key feature of our synthesis relied on the formation of highly substituted oxygenated tetrahydropyran using our silicon-directed [4 + 2]-annulation strategy. In addition, construction of the substituted (*E*,*E*)-diene through a modified Negishi cross-coupling demonstrated that this method can be useful for stereochemically challenging systems en route to complex molecule synthesis. Studies to further explore the scope and application of this strategy are currently underway.

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Supporting Information Available: Experimental details and selected spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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