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An Asymmetric Total Synthesis of Brevisamide

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Abstract

An enantioselective synthesis of marine alkaloid brevisamide was accomplished in a convergent manner. The synthesis utilized an enantioselective hetero-Diels-Alder reaction which sets three chiral centers in compound 11. The synthesis also features a modified Wolff-Kishner reduction, Rubottom oxidation and Suzuki-Miyaura coupling to furnish brevisamide.

The bloom of dinoflagellates causing 'Red Tide' led to the massive death of a wide range of marine life and human food poisoning in the Florida Coast and Gulf of Mexico.¹ Brevetoxins secreted by the dinoflagellate called *Ptychodiscus brevis* may have been responsible for this extensive natural calamity.² In 1981, Nakanishi and co-workers reported the structure of brevetoxin B, the first member of a new class of structurally extraordinary marine toxin.³ Brevetoxin consists of eleven contiguous trans-fused cyclic ether rings, spectacularly arranged in a 'ladder-like' rigid frame work.³ Nakanishi and coworkers subsequently proposed an intriguing biogenetic scheme indicating that brevetoxins may be biosynthesized by a poly-epoxide cascade cyclization.⁴

Further search for ladder-frame polyethers led to the discovery of brevenal (**1**) from *Karenia brevis*.⁵ Interestingly, this smaller polyether is antagonist to brevetoxins. Recently, Wright and co-workers have isolated a new marine alkaloid, brevisamide (**2**) from *K. brevis*, which appears to be the biogenetic template for the poly-epoxide cascade reaction leading to brevenal.⁶ It contains the same conjugated dienal side chain as brevenal (**1**) and a highly substituted tetrahydropyran similar to the first ring of brevenal. Thus, brevisamide appears to be an important biosynthetic precursor for the ladder-frame structures. Chemistry, biology and scarcity of natural abundance of brevisamide attracted our attention to its synthesis and subsequent design of molecular probes.⁷ Satake reported the first total synthesis based on a stepwise construction of the substituted tetrahydropyran ring and Suzuki-Miyaura coupling of the fragments.^{8a} Very recently, Lindsley and co-worker reported another route to brevisamide.^{8b} Herein we disclose an asymmetric total synthesis of brevisamide based upon a strategic facile assembly of the highly substituted tetrahydropyran ring using Jacobsen's asymmetric hetero-Diels-Alder reaction.⁹ The strategy renders high convergence and flexibility to structural modulation.

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Supporting Information Available: Experimental procedures and ¹H- and ¹³C-NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The retrosynthesis of our route is shown in Figure 2. Strategic bond disconnection of brevisamide provides a coupling reaction.¹⁰ The functionalized tetrahydropyran moiety **3** can be assembled through an asymmetric hetero-Diels-Alder reaction between the diene **5** and aldehyde **6** using Jacobsen's catalyst.^{9a} The resulting cycloadduct can be converted to **3** with a few additional steps of functional group manipulation. The other half of Suzuki-Miyaura coupling substrate is diene **4**. It could be easily constructed using Negishi's zirconium catalyzed carboalumination-iodination reaction¹¹ from a known starting material **7**.

The synthesis of functionalized tetrahydropyran moiety **3** is outlined in Scheme 1. The known aldehyde **8**¹² is converted to enone **9** via addition of ethylmagnesium bromide followed by Swern oxidation to provide **9** in 84% yield in two steps. It was treated with TESOTf in the presence of Et₃N to afford triethylsilyl diene **5** in 84% yield. Jacobsen's asymmetric catalytic hetero-Diels-Alder reaction of diene **5** and aldehyde **6** with 10 mol % Jacobsen's chromium catalyst **10**,^{9a} in the presence of molecular sieves 4 Å at 23 °C for 7 days afforded the desired cycloadduct **11** in 52% isolated yield. The Cycloadduct **11** was obtained with high diastereoselectivity (dr = 95%). The major diastereomer has shown high enantiomeric purity (ee = 96%). Of particular note, Jacobsen and co-workers have reported a very similar reaction with equally slow rate compared to other dienes.^{9b} Our synthetic strategy calls for the introduction of a hydroxyl group at the α position of the carbonyl group. This was achieved by Rubottom oxidation of **11** using *m*-chloroperoxybenzoic acid solution in toluene in the presence of aqueous NaHCO₃ buffer at 0 °C in 60% yield.¹³ Epoxidation proceeded from the less hindered side affording **12** as a single isomer. The stereochemical outcome of the Rubottom oxidation was confirmed by NOE experiment (see the supporting information).

The synthesis of functionalized tetrahydropyran derivative **3** is shown in Scheme 2. A modified Wolff-Kishner reduction¹⁴ protocol was utilized for the reduction of ketone **12**. Accordingly, ketone **12** was first converted to its corresponding hydrazone with tosylhydrazine in ethanol. The resulting hydrazone was reduced with NaBH₃CN under pH 3 to provide the corresponding hydrazine. Treatment of this hydrazine with NaOAc in EtOH at 75 °C, afforded deoxygenated product **13** in 76% yield for the three steps. Protection of the alcohol as TBS ether followed by removal of the benzyl ether by catalytic hydrogenation over 10 % Pd-C provided the alcohol **14** in 82% yield for the two steps. Mitsunobu reaction of alcohol **14** using hydrazoic acid as the azide source afforded the azide **15** in 94% yield.¹⁵ Reduction of the azide by catalytic hydrogenation followed by acetylation of the resulting amine furnished the acetamide. Selective desilylation of primary TBS-ether in this intermediate with a catalytic amount of pyridinium *p*-toluenesulfonate in ethanol at 23 °C provided a primary alcohol **16** in 77% yield for the two steps. The hydroxy ethyl derivative was converted to olefin **3** in two-step sequence using Grieco's protocol.¹⁶ Thus, alcohol **16** was reacted with *o*-nitrophenylselenenic cyanide and *n*-Bu₃P in THF at 23 °C to provide the corresponding phenylselenide derivative. Oxidation of selenide with *m*-CPBA resulted in olefin **3** in 50% yield for the two steps.

The synthesis of diene **4** is as shown in Scheme 3. The *E*-bromocrotyl alcohol **7**¹⁷ was reacted with trimethylsilylacetylene in DMF in the presence of diisopropylethylamine and a catalytic amount of Pd(PPh₃)₄ and CuI at 23 °C for 4 h to provide enyne derivative **17** in 96% yield.¹⁸ Desilylation of **17** with K₂CO₃ in methanol at 23 °C for 1 h afforded alkynol **18** in 82% yield. It was treated with trimethylaluminum in the presence of catalytic amount of dichlorozirconocene for 24 h. Subsequent treatment of the reaction mixture with elemental iodine provided the desired diene **19** in 39% yield.¹⁹ Treatment of **19** with TBSCl and imidazole furnished silyl ether **4** in 87% yield.

Scheme 4 depicts the synthesis of brevisamide by assembly of tetrahydropyran **3** and vinyl iodide **4** using a Suzuki-Miyaura coupling reaction as the key step as utilized by Satake and co-workers.⁹ The requisite alkylborane was generated *in situ* by hydroboration of **3** with 9-

BBN (5 equiv) in THF at 23 °C. After 3 h, the resulting solution containing the alkylborane was carefully treated with a degassed saturated aqueous Cs₂CO₃ solution. The cross-coupling of the resulting alkylborane and iodide **4** using a catalytic amount of PdCl₂(dppf)·CH₂Cl₂ at 45 °C in the presence of additional DMF yielded a TBS-ether intermediate. This intermediate was desilylated to give **20** in 40% yield for the two steps. Selective oxidation of the allylic alcohol in **20** was carried out using TEMPO in the presence of PhI(OAc)₂ in CH₂Cl₂ at 23 °C for 1 h. This has provided synthetic brevisamide **2** [$[\alpha]_D^{20} = -14.5$ (c 0.30, MeOH)] and those of natural brevisamide⁷ [$[\alpha]_D^{22} = -13$ (c 0.18, MeOH)] are identical.

In summary, we have reported an asymmetric total synthesis of (–)-brevisamide in 22 total synthetic steps, with an unoptimized yield of 1.7% in **18** longest linear steps from the readily prepared aldehyde **8**. Substituted tetrahydropyran fragment of brevisamide was synthesized in enantiomerically pure form using Jacobsen's asymmetric hetero-Diels-Alder reaction. This reaction has set three of the four stereocenters of brevisamide enantioselectively. The vinyl iodide fragment **4** was readily prepared using Negishi's zirconium catalyzed carboalumination-iodination reaction. The synthesis also features Suzuki-Miyaura cross coupling and selective allylic oxidation using TEMPO. The present synthesis will provide access to a variety of structural analogues of brevisamide for further studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Brevenal (1)

Brevisamide (2)

Figure 1.
Structures of brevenal (1) and brevisamide (2)

Figure 2.
Retrosynthetic analysis of **2**

Scheme 1.
Synthesis of dihydro-2H-pyranone **12**.

Scheme 2.
Synthesis of tetrahydropyran **3**.

Scheme 3.
Synthesis of diene **4**.

Scheme 4.
Synthesis of brevisamide 2.