## An Asymmetric Total Synthesis of Brevisamide

## Arun K. Ghosh\* and Jianfeng Li

Departments of Chemistry and Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907

akghosh@purdue.edu

Received July 23, 2009

## ORGANIC LETTERS 2009 Vol. 11, No. 18 4164-4167

## 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" has led to the massive death of a wide range of marine life and human food poisoning in the Florida Coast and Gulf of Mexico.<sup>1</sup> Brevetoxins secreted by the dinoflagellate *Ptychodiscus brevis* may have been responsible for this extensive natural calamity.<sup>2</sup> In 1981, Nakanishi and co-workers reported the structure of brevetoxin B, the first member of a new class of structurally extraordinary marine toxins.<sup>3</sup> Brevetoxin consists of 11 contiguous trans-fused cyclic ether rings, spectacularly arranged in a "ladder-like" rigid framework.<sup>3</sup> Nakanishi and co-workers subsequently proposed an intriguing biogenetic scheme indicating that brevetoxins may be biosynthesized by a polyepoxide cascade cyclization.<sup>4</sup>

A further search for ladder-frame polyethers led to the discovery of brevenal (1) from *Karenia brevis*.<sup>5</sup> Interestingly, this smaller polyether is an antagonist of 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 polyepoxide cascade reaction leading to brevenal.<sup>6</sup> It contains the same conjugated dienal side chain as brevenal (**1**) and a highly substituted tetrahydropyran similar to the first ring of brevenal (Figure 1). Thus, brevisamide appears to be an important biosynthetic precursor for the ladder-frame structures. Chemistry, biology, and scarcity of the natural abundance of brevisamide attracted



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

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our attention to its synthesis and subsequent design of molecular probes.<sup>7</sup> Satake reported the first total synthesis based on a stepwise construction of the substituted tetrahydropyran ring and Suzuki–Miyaura coupling of the fragments.<sup>8a</sup> Very recently, Lindsley and co-worker reported another route to brevisamide.<sup>8b</sup> 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.<sup>9</sup> The strategy renders high convergence and flexibility to structural modulation.





The retrosynthesis of our route is shown in Figure 2. Strategic bond disconnection of brevisamide provides a coupling reaction.<sup>10</sup> The functionalized tetrahydropyran moiety **3** can be assembled through an asymmetric hetero-Diels–Alder reaction between diene **5** and aldehyde **6** using Jacobsen's catalyst.<sup>9a</sup> The resulting cycloadduct can be converted to **3** with a few additional steps of functional group manipulation. The other half of the Suzuki–Miyaura coupling partner is diene **4**. It could be easily constructed using Negishi's zirconium-catalyzed carboalumination—iodination reaction<sup>11</sup> from the known starting material **7**.

The synthesis of the functionalized tetrahydropyran moiety **3** is outlined in Scheme 1. Aldehede  $8^{12}$  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 Et<sub>3</sub>N to afford

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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,<sup>9a</sup> in the presence of molecular sieves (4 Å) at 23 °C for 7 days, afforded the desired cycloadduct 11 in 52% isolated yield. 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 an equally slow rate compared to other dienes.<sup>9b</sup> Our synthetic strategy calls for the introduction of a hydroxyl group at the  $\alpha$  position of the carbonyl group in **12**. This was achieved by Rubottom oxidation of 11 using mchloroperoxybenzoic acid solution in toluene in the presence of aqueous NaHCO<sub>3</sub> buffer at 0 °C in 60% yield.<sup>13</sup> 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 reduction<sup>14</sup> 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 NaBH<sub>3</sub>CN 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. Pro-

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tection 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.<sup>15</sup> Reduction of the azide by catalytic hydrogenation followed by acetylation of the resulting amine furnished the acetamide. Selective desilylation of the primary TBS-ether in this intermediate with a catalytic amount of pyridinium ptoluenesulfonate in ethanol at 23 °C provided primary alcohol 16 in 77% yield for the two steps. The hydroxy ethyl derivative was converted to olefin 3 in a two-step sequence using Grieco's protocol.<sup>16</sup> Thus, alcohol 16 was reacted with o-nitrophenylselenic cyanide and n-Bu<sub>3</sub>P in THF at 23 °C to provide the corresponding phenylselenide derivative. Oxidation of the 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**<sup>17</sup> was reacted with trimethylsilylacetylene in DMF in the presence of diisopropylethylamine and a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI at 23 °C for 4 h to provide enyne derivative **17** in 96% yield.<sup>18</sup> Desilylation of **17** with K<sub>2</sub>CO<sub>3</sub> in methanol at 23 °C for 1 h afforded alkynol **18** in 82% yield. It was treated with trimethylaluminum in the presence of a catalytic amount of dichlorozir-

<sup>(18)</sup> Sonogashira, K.; Tohda, Y.; Hagihara, N. Tetrahedron Lett. 1975, 16, 4467–4470.





conocene for 24 h. Subsequent treatment of the reaction mixture with elemental iodine provided the desired diene **19** in 39% yield.<sup>19</sup> 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.<sup>9</sup> 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  $Cs_2CO_3$  solution. The cross-coupling of the resulting alkylborane and iodide **4** using a catalytic amount of PdCl<sub>2</sub>-(dppf)·CH<sub>2</sub>Cl<sub>2</sub> at 45 °C in the presence of additional DMF

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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)<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 23 °C for 1 h. This provided synthetic brevisamide **2** in 87% isolated yield. The spectroscopic data of synthetic brevisamide **2**  $[[\alpha]_D^{20} = -14.5 (c \ 0.30, MeOH)]$  and those of natural brevisamide<sup>7</sup>  $[[\alpha]_D^{22} = -13 (c \ 0.18, MeOH)]$  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**. A 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.

Acknowledgment. Financial support by the National Institutes of Health is gratefully acknowledged. The authors thank David Anderson and Khriesto Shurrush (both Purdue University) for the experimental assistance.

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

OL901691D