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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

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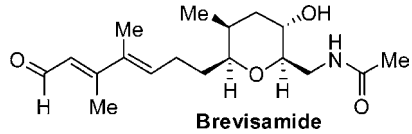
ABSTRACT

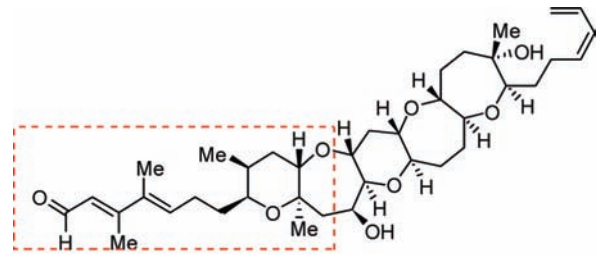


Brevisamide

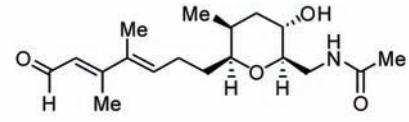
An enantioselective synthesis of marine alkaloid brevisamide was accomplished in a convergent manner. The synthesis utilized an enantioselective hetero-Diels−Alder reaction which sets three chiral centers in compound 11. The synthesis also features a modified Wolff−Kishner reduction, Rubottom oxidation, 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.[1] Brevetoxins secreted by the dinoflagellate *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 toxins.[3] Brevetoxin consists of 11 contiguous trans-fused cyclic ether rings, spectacularly arranged in a "ladder-like" rigid framework.[3] Nakanishi and co-workers subsequently proposed an intriguing biogenetic scheme indicating that brevetoxins may be biosynthesized by a polyepoxide cascade cyclization.[4]

A further search for ladder-frame polyethers led to the discovery of brevenal (**1**) from *Karenia brevis*.[5] 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.[6] 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



Brevenal (1)



Brevisamide (2)

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

(1) (a) *Topics in Current Chemistry*; Scheuer, P. J., Ed.; Springer-Verlag: Heidelberg, 1993; Vol. 167. (b) *Topics in Heterocyclic Chemistry*; Kiyota, H., Ed.; Springer-Verlag: Berlin Heidelberg, 2006; Vol. 5.

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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.

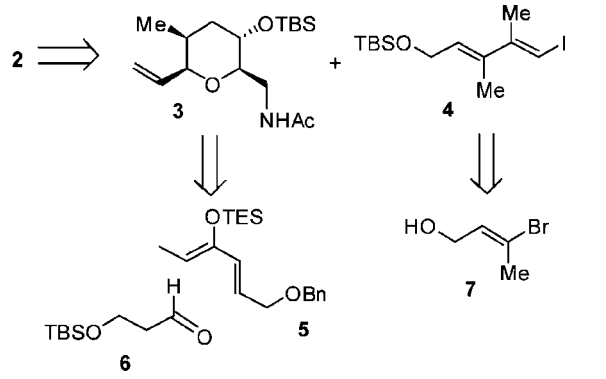
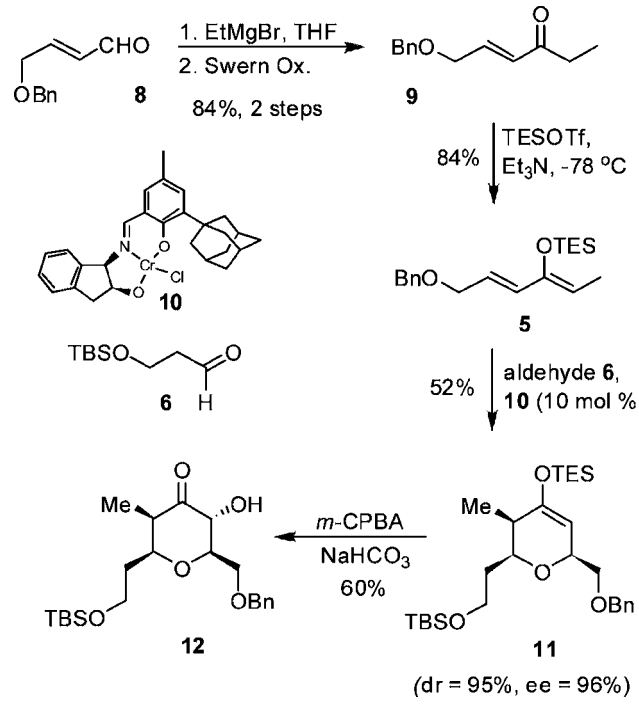


Figure 2. Retrosynthetic analysis of **2**.

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 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 the Suzuki−Miyaura coupling partner is diene **4**. It could be easily constructed using Negishi's zirconium-catalyzed carboalumination−iodination reaction[11] 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_3N to afford

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



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. 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.[9b] Our synthetic strategy calls for the introduction of a hydroxyl group at the α position of the carbonyl group in **12**. This was achieved by Rubottom oxidation of **11** using *m*-chloroperoxybenzoic acid solution in toluene in the presence of aqueous $NaHCO_3$ 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 reduction[14] 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 $NaBH_3CN$ 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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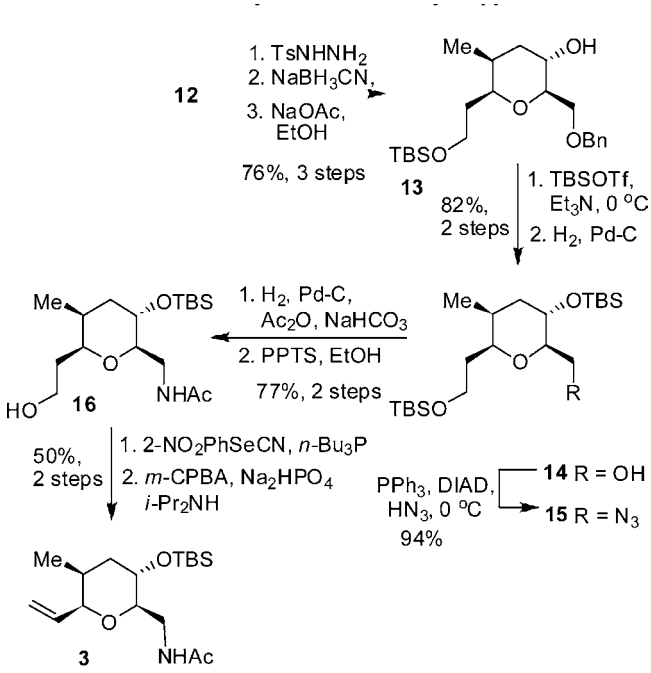
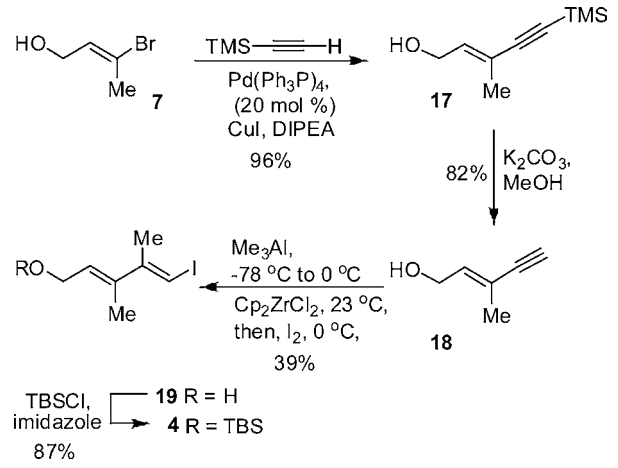
Scheme 2. Synthesis of Tetrahydropyran **3**



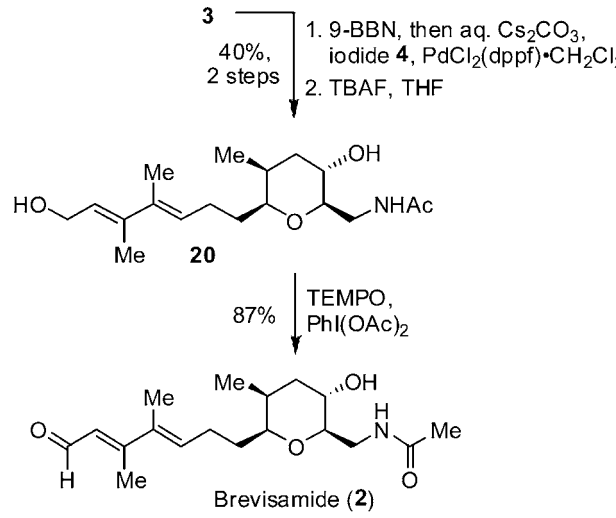
Scheme 3. Synthesis of Diene **4**



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.[15] 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 *p*-toluenesulfonate 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.[16] Thus, alcohol **16** was reacted with *o*-nitrophenylselenic cyanide and *n*-Bu_3P 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**[17] was reacted with trimethylsilylacetylene in DMF in the presence of diisopropylethylamine and a catalytic amount of $Pd(PPh_3)_4$ and CuI at 23 °C for 4 h to provide enyne derivative **17** in 96% yield.[18] Desilylation of **17** with K_2CO_3 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 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. Synthesis of Brevisamide **2**



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 Cs_2CO_3 solution. The cross-coupling of the resulting alkylborane and iodide **4** using a catalytic amount of $PdCl_2$-(dppf)•CH_2Cl_2 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 $PhI(OAc)_2$ in CH_2Cl_2 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[7] [$[\alpha]_D^{22} = -13$ (*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.

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

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