Published in final edited form as:

Org Lett. 2009 September 3; 11(17): 3950–3952. doi:10.1021/ol9015755.

Total Synthesis of Brevisamide

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Abstract

The second total synthesis of Brevisamide, a marine cyclic ether alkaloid from *Karenia brevis* is reported. This streamlined synthesis proceeds in 21 steps, 14 steps longest linear sequence, in 5.2% overall yield and features a key SmI₂ reductive cyclization step to access the tetrasubstituted pyran core.

Recently, Satake, Tachibana, Wright and co-workers reported on the isolation and characterization of brevisamide (**1**), an unprecedented monocyclic ether alkaloid, from the dinoflagellate *Karenia brevis*, a species known to produce polycyclic ether toxins such as the brevetoxins.¹ Identification of **1**, containing the same conjugated 3,4-dimethyl-2,4-dienal side chain as the more complex polycyclic ether brevenal,² provided further support for the model of ladder-frame initiation in the synthesis of polycyclic ether natural products, and thus has garnered significant synthetic interest.¹ Within months of the publication of the isolation and characterization of brevisamide (**1**), the first total synthesis and structural confirmation of **1** was reported by the same group.³ The synthesis proceeded in 28 steps, with the longest linear sequence of 21 steps, for an overall yield of **1** from *cis*-but-2-ene diol of 0.23%.³ In this letter, we wish to report our efforts on the total synthesis of brevisamide (**1**) employing a fundamentally different synthetic strategy that afforded **1** in 21 total synthetic steps and an overall yield of 5.2%.

Scheme 1 illustrates our retrosynthetic analysis of **1**, providing a convergent synthetic strategy. Inspired by the elegant synthesis of brevenal by Takamura and coworkers,⁴ we envisioned the western C₁-C₄ side chain would be installed through a Horner-Emmons-Wadsworth reaction utilizing **2**, prepared from commercially available **4**. Key pyran **3**, the C₅-C₁₅ fragment, was conceived to be derived from **5** through a SmI₂-mediated reductive cyclization reaction.⁵⁻¹⁰

The synthesis of pyran **3** is described in Scheme 2. Mono-benzyl protected-1,4-butane diol **6** was oxidized under Swern conditions to the corresponding aldehyde which was then subjected to a Brown crotylation reaction to afford **7** as a single diastereomer in 87% ee.^{11,12} Hydroboration and chemoselective TBS protection of the primary alcohol provided **8** in 89% yield for the two steps. 1,4-addition of **8** to ethyl propiolate proved difficult, resulting in

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Supporting Information Available: Experimental procedures, characterization data, 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>.

complex mixtures under a number of reaction conditions.¹³ Ultimately, slow addition of ethyl propiolate *via* syringe pump over 24 hours delivered the key intermediate **9** in 93% isolated yield. Removal of the TBS group proved equally problematic. Upon exposure to TBAF, a 1:1 mixture of the desired **10** and an unanticipated 1,3-dioxepane **11** formed. While separable, this undesired side product was detrimental at this stage of the synthesis. After surveying a variety of reaction conditions, we found that addition of a few drops of concentrated HCl in MeOH at 0 °C smoothly delivered the alcohol **10** in quantitative yield. Swern oxidation proceeded uneventfully delivering the key template for the reductive cyclization.⁵⁻¹⁰ In the event, exposure to SmI₂ provided the desired pyran **12** in 69% yield for the three steps. The relative stereochemistry of **12** was assigned by NMR and nOe analysis, and in agreement with literature precedent.⁵⁻¹⁰

Once in hand, the secondary alcohol of **12** was protected and the ester hydrolyzed to produce acid **13** in 85% yield for the two steps. Curtius rearrangement with (PhO)₂P(O)N₃ (DPPA) provided the aminomethyl congener **14** in 81% yield.^{14,15} Finally, an acetylation, benzyl deprotection and oxidation sequence afforded target pyran **3**, the C₅-C₁₅ fragment, in 81% yield for the three steps. Thus, the longest linear sequence, 13 steps, was completed in 14.9% overall yield.

Attention now focused on the synthesis of phosphonate ester **2**.⁴ As shown in Scheme 3, a Wittig reaction with 3-hydroxybutan-2-one **4**, and subsequent bromination, generates the secondary bromide **15** in 90% yield for the two steps. Application of an Arbuzov reaction delivers the key phosphoate ester **2**, the C₁-C₄ side chain, in 92% yield.^{4,16}

The Horner-Wadsworth-Emmons reaction between the C₁-C₄ fragment **2** and the C₅-C₁₅ fragment **3** proceeded well, installing the conjugated 3,4-dimethyl-2,4-dienal moiety and delivering **16** in 78% yield (Scheme 4). DIBALH reduction of the ester to the corresponding allylic alcohol⁴ and TBAF-mediated deprotection of the secondary TBS ether delivered **17**, the direct precursor to brevisamide, in 71% yield for the two steps. A final MnO₂ oxidation of the allylic alcohol produced the natural product brevisamide (**1**) in 74% yield. The synthetic **1** exhibited physical and spectroscopic data identical to that of the natural brevisamide and that of the previously prepared synthetic brevisamide.^{1,3,17}

Thus, the second total synthesis of brevisamide (**1**) has been accomplished in 21 synthetic steps, with 14 steps longest linear sequence, and an overall yield from mono-benzyl protected-1,4-butane diol **6** of 5.2%. Noteworthy synthetic steps from this route include a SmI₂ reductive cyclization to generate the highly functionalized pyran **3** and a Horner-Wadsworth-Emmons reaction to assemble the western C₁-C₄ **2** and eastern C₅-C₁₅ **3** fragments. With a high-yielding synthetic route in place, future efforts will focus on the synthesis of unnatural brevisamide analogs and attempts to employ **1** in the biomimetic, ladder-frame initiated synthesis of more complex polyethers. These efforts are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported, in part, by the Department of Pharmacology and Vanderbilt University. Funding for the NMR instrumentation was provided in part by a grant from NIH (S10 RR019022). The authors thank Dr. Kyle Emmitte (Vanderbilt University) for helpful conversations.

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17. See Supporting Information for full details.

Scheme 1.
Retrosynthetic analysis of brevisamide (**1**)

Scheme 2.
 Synthesis of tetra-substituted pyran **3**.

Scheme 3.
Synthesis of phosphonate ester **2**

Scheme 4.
Completion of the synthesis of brevisamide (**1**).