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Total Synthesis of Brevisamide

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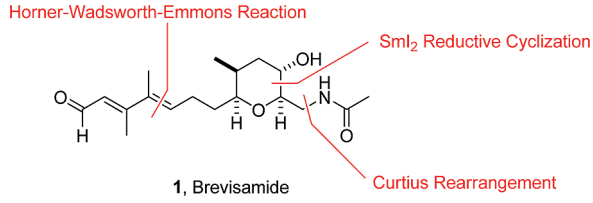
ABSTRACT

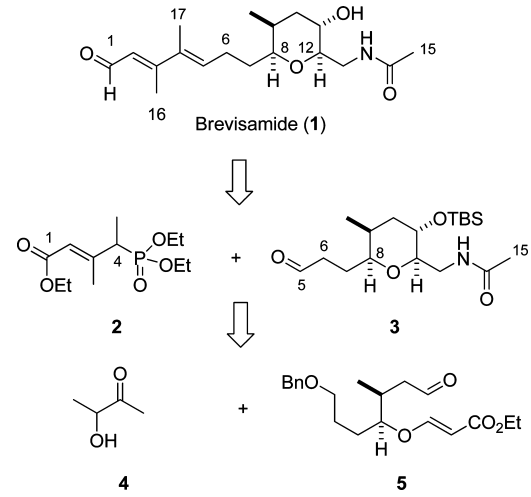


The second total synthesis of Brevisamide, a marine cyclic ether alkaloid from *Karenia brevis*, is reported. This streamlined synthesis proceeds in 21 steps, 14 steps longest linear sequence, in 5.2% overall yield and features a key SmI_2 reductive cyclization step to access the tetrasubstituted pyran core.

Recently, Satake, Tachibana, Wright, and co-workers reported on the isolation and characterization of brevisamide (**1**), an unprecendented monocylic 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 polycylic 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 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 co-workers,[4] we envisioned the western C_1-C_4 side chain would be installed through a Horner−Emmons−Wadsworth reaction

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



(1) Satake, M.; Bourdelais, A. J.; Van Wagoner, R. M.; Baden, D. G.; Wright, J. L. C. *Org. Lett.* **2008**, *10*, 3465–3468.
(2) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M., Jr.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2–6.
(3) Kuranaga, T.; Shirai, T.; Baden, D. G.; Wright, J. L. C.; Satake, M.; Tachibana, K. *Org. Lett.* **2009**, *11*, 217–220.
(4) Takamura, H.; Kikuchi, S.; Nakamura, Y.; Yamagami, Y.; Kishi, T.; Kadota, I.; Yamamoto, Y. *Org. Lett.* **2009**, *11*, 2531–2534.

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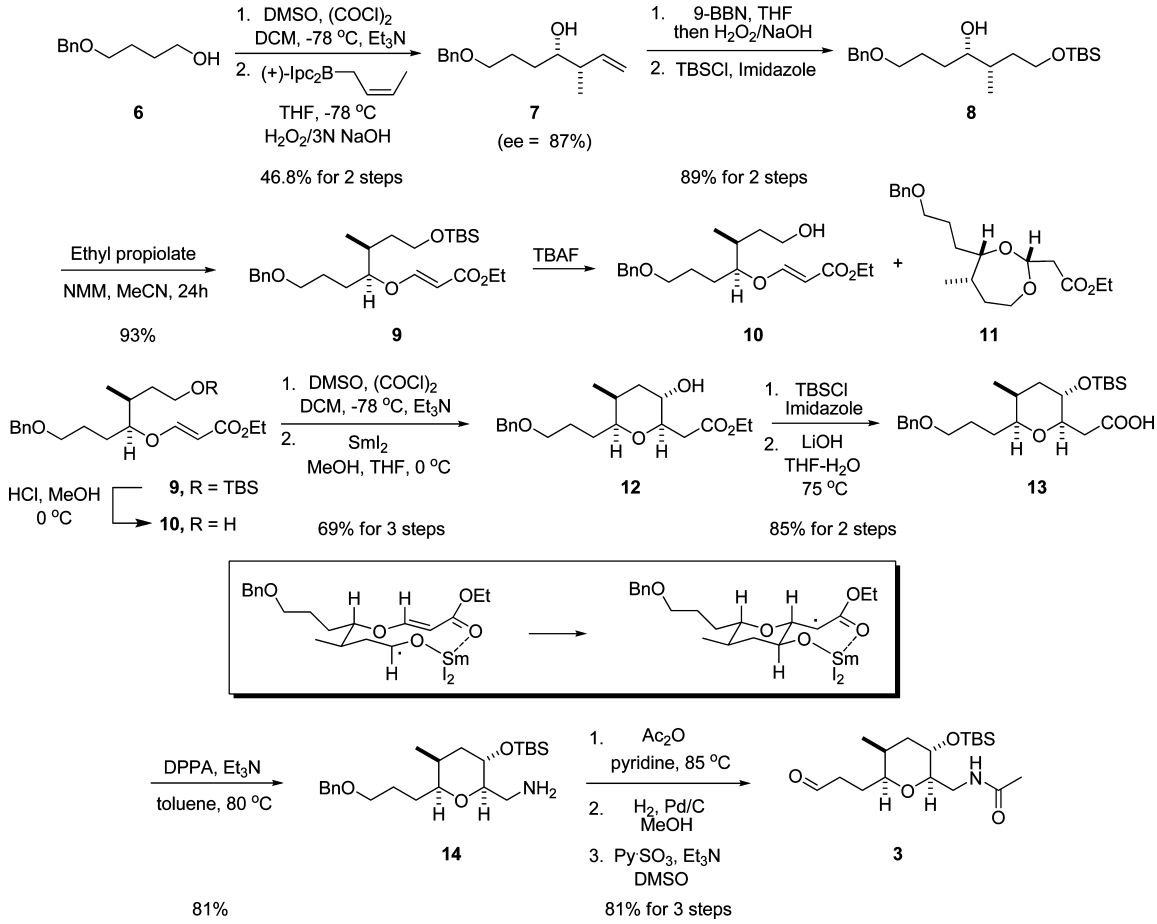
Scheme 2. Synthesis of Tetra-Substituted Pyran **3**



utilizing **2**, prepared from commercially available **4**. Key pyran **3**, the C_5-C_{15} fragment, was conceived to be derived from **5** through a SmI_2-mediated reductive cyclization reaction.[5−10]

The synthesis of pyran **3** is described in Scheme 2. Monobenzyl 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 complex mixtures under a number of reaction conditions.[13] Ultimately, slow addition of ethyl propiolate via syringe pump over 24 h 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 SmI_2 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 rearragement with $(PhO)_2P(O)N_3$ (DPPA) provided the aminomethyl congener **14** in 81% yield.[14,15] Finally, an acetylation, benzyl deprotection, and oxidation sequence afforded target pyran **3**, the C_5-C_{15} fragment, in 81% yield for the three steps. Thus, the longest

(5) Gillmann, T. *Tetrahedron Lett.* **1993**, *34*, 607–610.
(6) Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahderon Lett.* **2002**, *43*, 8653–8655.
(7) McErlean, C. S. P.; Willis, A. C. *Synlett* **2009**, *2*, 233–236.
(8) Clark, S. J.; Hayes, S. T.; Blake, A. J.; Gobbi, L. *Tetrahedron Lett.* **2007**, *48*, 2501–2503.
(9) Saito, T.; Kimishima, A.; Nakata, T. *Heterocycles* **2006**, *70*, 177–180.
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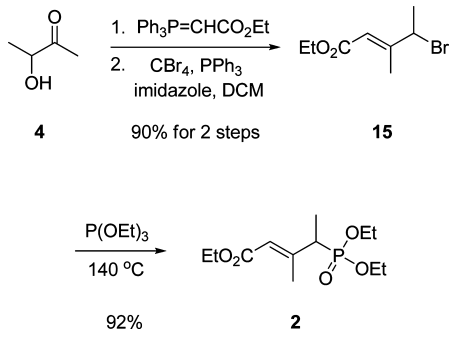
(12) Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4612–4617.
(13) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047–5050.
(14) Davis, M. C. *Synth. Commun.* **2007**, *37*, 3519–3528.
(15) Leogane, O.; Lebel, H. *SYNTHESIS* **2009**, *11*, 1935–1940.

linear sequence, 14 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

Scheme 3. Synthesis of Phosphonate Ester **2**



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 C_1-C_4 side chain, in 92% yield.[4,16]

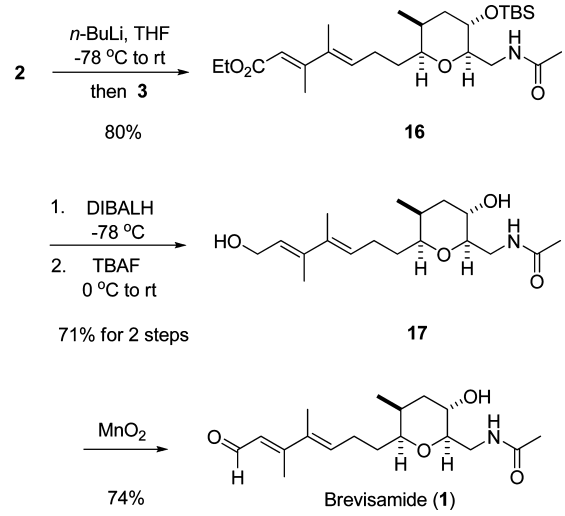
The Horner−Wadsworth−Emmons reaction between the C_1-C_4 fragment **2** and the C_5-C_{15} fragment **3** proceeded well, installing the conjugated 3,4-dimethyl-2,4-dienal moiety and delivering **16** in 78% yield (Scheme 4). DIBALH reduction of the ester to the corresponding allylic alcohol[4] and TBAF-mediated deprotection of the secondary TBS ether delivered **17**, the direct precursor to brevisamide, in 71% yield for the two steps. A final MnO_2 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 monobenzyl protected-1,4-butane diol **6** of 5.2%. Noteworthy synthetic

(16) Alen, J.; Dobrzanska, L.; De Morggraeve, W. M.; Compernolle, F. *J. Org. Chem.* **2007**, *72*, 1055–1057.

(17) See Supporting Information for full details.

Scheme 4. Completion of the Synthesis of Brevisamide (**1**)



steps from this route include a SmI_2 reductive cyclization to generate the highly functionalized pyran **3** and a Horner−Wadsworth−Emmons reaction to assemble the western C_1-C_4 **2** and eastern C_5-C_{15} **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.

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Supporting Information Available: Experimental procedures, characterization data, 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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