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Total Synthesis of (−)-Brevisin: A Concise Synthesis of a New Marine Polycyclic Ether

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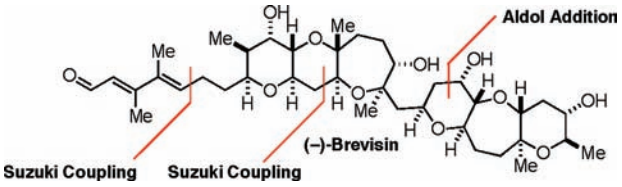
ABSTRACT



The first and highly efficient total synthesis of (−)-brevisin has been achieved. The title compound was synthesized in only 29 steps (longest linear sequence) from commercially available starting materials. The synthesis provided over 70 mg of a marine polycyclic ether compound.

The polycyclic ether (−)-brevisin[1] (**1**, Figure 1) was isolated from the red tide dinoflagellate *Karenia brevis*, which produces a variety of polycyclic ethers such as the brevetoxins,[2] brevenal,[3] and the monocyclic ether amide brevisamide.[4] Brevisin's unique structure consists of two fused tricyclic ether ring assemblies bridged by a methylene carbon and a conjugated aldehyde side chain, which is similar to the side chain in brevenal and bevisamide. Interestingly, despite **1** having a unique structure, which is divided into two tricyclic ether units by the methylene, **1** inhibits the binding of tritiated 42-dihydrobrevetoxin B (PbTx-3) to the voltage sensitive sodium channels.[1a] However, as with the other marine polycyclic ethers, the biological activities of **1** have not been fully investigated due to the extremely small supply from natural sources. In order to elucidate its interaction with a target protein and test other biological activities, such as mouse lethality and cytotoxicity, the chemical synthesis for

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(1) (a) Satake, M.; Campbell, A.; Van Wagoner, R. M.; Bourdelais, A. J.; Jacocks, H.; Baden, D. G.; Wright, J. L. C. *J. Org. Chem.* **2009**, *74*, 989. (b) Van Wagoner, R. M.; Satake, M.; Bourdelais, A. J.; Baden, D. G.; Wright, J. L. C. *J. Nat. Prod.* **2010**, *73*, 1177. (c) Kuranaga, T.; Satake, M.; Baden, D. G.; Wright, J. L. C.; Tachibana, K. *Tetrahedron Lett.* **2010**, *51*, 4673.

(2) (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 514. (c) Baden, D. G.; Bourdelais, A. J.; Jacocks, H.; Michelliza, S.; Naar, J. *J. Environ. Health Perspect.* **2005**, *113*, 621.

(3) (a) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M., Jr; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2. (b) The proposed structure was revised: Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989.

(4) (a) Satake, M.; Bourdelais, A. J.; Van Wagoner, R. M.; Baden, D. G.; Wright, J. L. C. *Org. Lett.* **2008**, *10*, 3465. We have successfuly synthesized brevisamide and tested its biological activities:(b) Kuranaga, T.; Shirai, T.; Baden, D. G.; Wright, J. L. C.; Satake, M.; Tachibana, K. *Org. Lett.* **2009**, *11*, 217. (c) Tsutsumi, R.; Kuranaga, T.; Wright, J. L. C.; Baden, D. G.; Ito, E.; Satake, M.; Tachibana, K. *Tetrahedron* **2010**, *66*, 6775.

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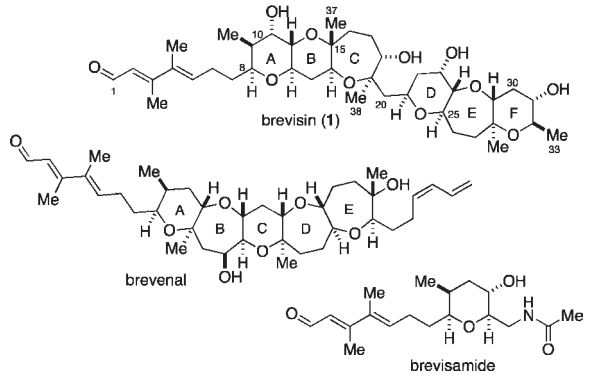
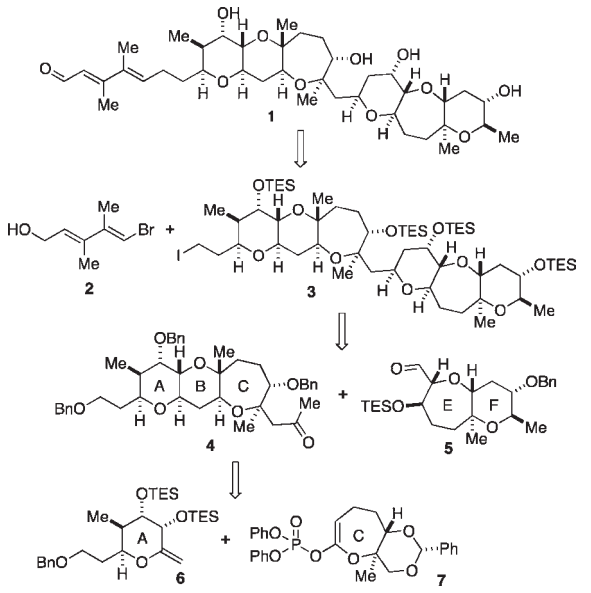


Figure 1. Structures of brevisin (**1**), brevenal, and brevisamide.

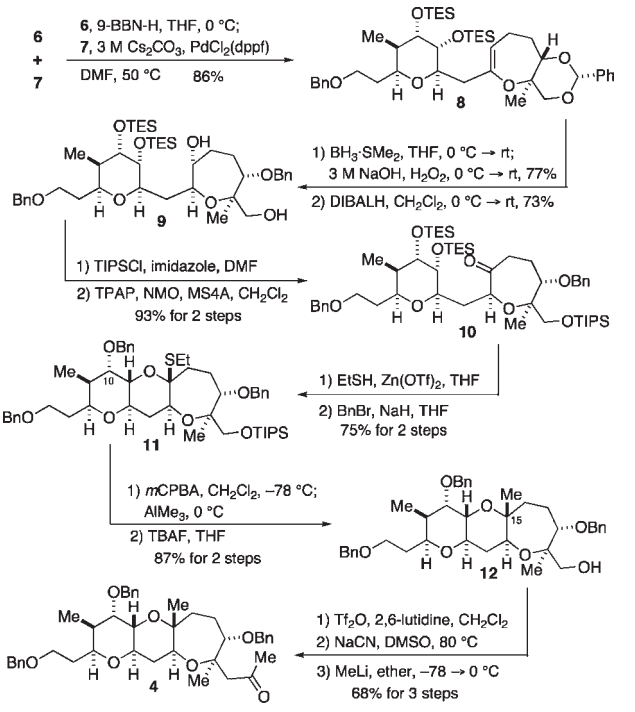
supplying materials was essential. Here we report the first and highly efficient total synthesis of **1** using Suzuki−Miyaura cross coupling and an aldol addition as the key steps.

Scheme 1. Synthetic Plan of **1**



Our synthetic strategy to **1** is summarized in Scheme 1. The side chain fragment **2**[4c,5] and iodide fragment **3** would be connected by means of Suzuki−Miyaura cross coupling. The polycyclic ether core would be synthesized from the ABC-ring methyl ketone **4** and the EF-ring aldehyde **5** by an aldol addition and subsequent construction of the D-ring. Tricyclic ether **4** would be synthesized from the A-ring exocyclic enol ether **6**[6] and the C-ring ketene acetal phosphate **7** by our Suzuki−Miyaura cross-coupling-based strategy.[7]

Scheme 2. Synthesis of the ABC Ring Fragment



The A-ring fragment **6** was connected by Suzuki−Miyaura cross coupling to the C-ring ketene acetal phosphate **7**, which was prepared in eight steps[1c,8] from commercially available 2-deoxy-D-ribose. Namely hydroboration of **6** with 9-BBN generated a corresponding alkylborane, which was reacted in situ with **7** in the presence of aqueous Cs_2CO_3 and a catalytic amount of $PdCl_2(dppf)$ giving rise to a cross-coupled product **8** in 86% yield. Successive hydroboration/oxidation of **8** with $BH_3 \cdot SMe_2$ followed by regioselective DIBALH reduction[9] gave diol **9**. The primary alcohol of diol **9** was selectively protected with a TIPS group, and then the secondary alcohol was oxidized to the ketone **10** using TPAP−NMO.[10] Treatment of **10** with $Zn(OTf)_2$ in the presence of EtSH accomplished the deprotection of the TES groups and mixed thioacetal formation, and subsequent benzylation of the hydroxy group at C-10 afforded mixed thioacetal **11**. Mixed thioacetal **11** was oxidized to the corresponding sulfone, which was treated with $AlMe_3$ in a one-pot manner[11] to introduce the C-15 methyl group. Then, subsequent deprotection of

(5) Shirai, T.; Kuranaga, T.; Wright, J. L. C.; Baden, D. G.; Satake, M.; Tachibana, K. *Tetrahedron Lett.* **2010**, *51*, 1394.

(6) Ohtani, N.; Tsutsumi, R.; Kuranaga, T.; Shirai, T.; Wright, J. L. C.; Baden, D. G.; Satake, M.; Tachibana, K. *Heterocycles* **2010**, *80*, 825.

(7) (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075. (c) Sasaki, M.; Fuwa, H. *Nat. Prod. Rep.* **2008**, *25*, 401.

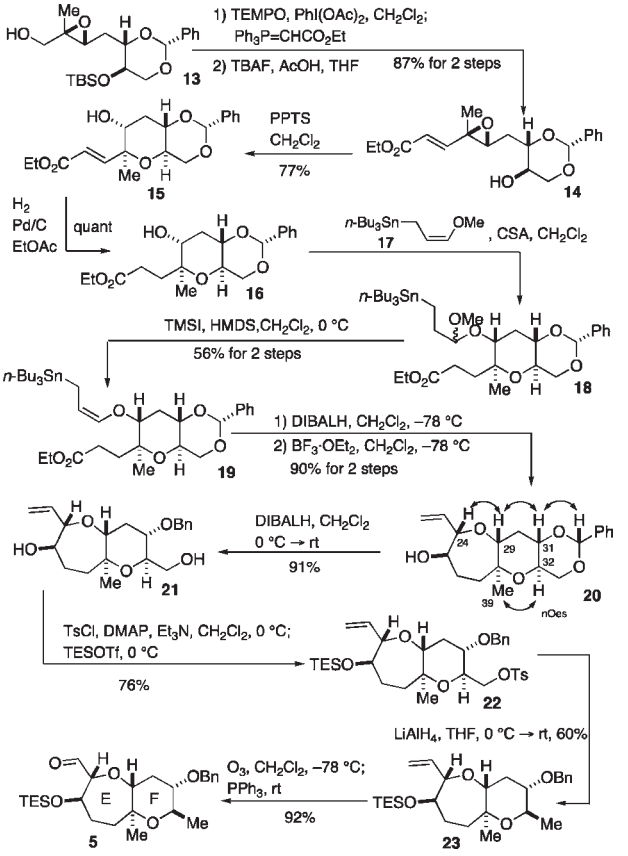
(8) Kadota, I.; Kadowaki, C.; Park, C.-H.; Takamura, H.; Sato, K.; Chan, P. W. H.; Thorand, S.; Yamamoto, Y. *Tetrahedron* **2002**, *58*, 1799.

(9) Takano, S.; Akiyama, Y.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, *12*, 1593.

(10) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639.

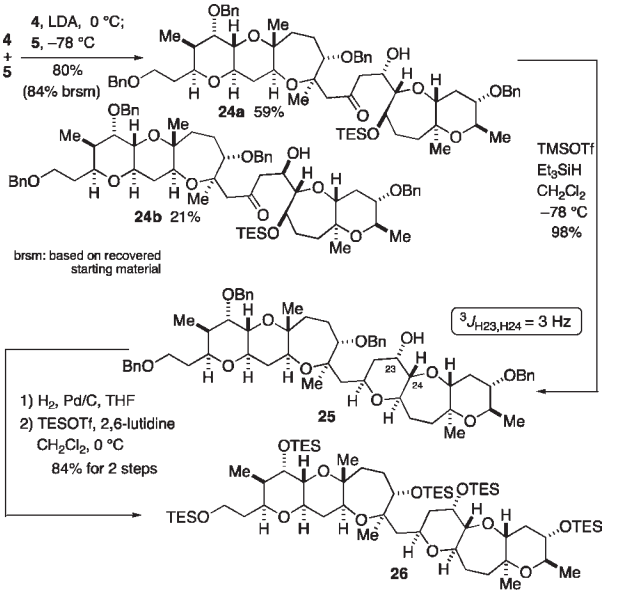
the TIPS group gave the alcohol **12**. Triflation of **12** followed by cyanidation with NaCN led to the corresponding nitrile, which was treated with MeLi to afford the methyl ketone **4** in 68% yield from **12** (Scheme 2).

Scheme 3. Synthesis of the EF Ring Fragment



The synthesis of the EF-ring fragment **5** started from the known hydroxy epoxide **13**.[12] A one-pot oxidation/Wittig reaction[13] of **13** followed by the deprotection of the TBS group led to α,β-unsaturated ester **14**. Treatment of **14** with a catalytic amount of PPTS induced 6-*endo* cyclization[12] to afford the pyran **15**, and subsequent hydrogenation of **15** led to ester **16**. Methyl acetal formation of **16** with γ-methoxyallylstannane **17**[14] provided mixed methyl acetal **18** as a mixture of the diastereomers. This mixture was treated with HMDS and TMSI to afford allylstannane **19**. Reduction of the ester to the corresponding aldehyde by DIBALH and treatment with $BF_3 \cdot OEt_2$ accomplished intramolecular allylation[15] to give the oxepane **20**. The relative configuration of **20** was confirmed by observed NOE correlations between H-24/H-29, H-29/H-31, and H_3-39/H-32 and by the large proton coupling constant (8.8 Hz) between H-31 and H-32. The regioselective DIBALH reduction of **20** led to diol **21**. The primary alcohol of diol **21** was selectively tosylated, and then the secondary alcohol was protected by a TES group to afford tosylate **22**. The tosylate **22** was reduced by $LiAlH_4$ to afford the EF-ring compound **23**. Finally, ozonolysis of **23** provided the aldehyde **5** (Scheme 3).

Scheme 4. Synthesis of the ABC/DEF Ring Compound **26**



The connection of **4** and **5** by aldol addition and construction of the polycyclic ether core were accomplished as shown in Scheme 4. Treatment of the lithium enolate derived from **4** with aldehyde **5** furnished a separable 2.8:1 mixture of C-23 diastereomers **24a**[16] and **24b**.[17] Treatment of **24a** with Et_3SiH in the presence of TMSOTf[18] led to deprotection of TES ether with concomitant stereoselective reduction to cyclized product **25** in 98% yield. The unprecedented polycyclic ether core of **1** could be constructed in only two steps from the key fragments **4** and **5**. Removal of all benzyl groups of **25** followed by reprotection with the TES group afforded pentakis TES ether **26**. At this stage, in order to convert **26** to iodide **3**, only primary TES ether

(11) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.

(12) Hydroxy epoxide **13** was synthesized by five steps from commercially available 2-deoxy-D-ribose: Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.

(13) Vatele, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715.

(14) Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6597.

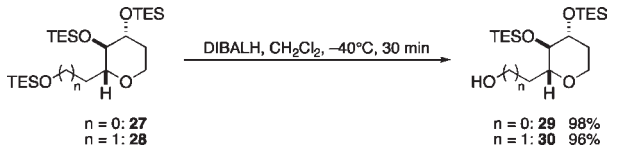
(15) (a) Yamamoto, Y.; Yamada, J.; Kadota, I. *Tetrahedron Lett.* **1991**, *32*, 7069. (b) Gevorgyan, V.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 1313. (c) Kadota, I.; Kawada, M.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 7439.

(16) The stereochemistry of the newly generated hydroxy group at the C-23 of **24a** was assigned after construction of the D ring. The coupling constant (3 Hz) between H-23 and H-24 in **25** indicated the axial orientation of the hydroxy group at the C-23.

(17) The minor undesired C-23 diastereomer **24b** could also be converted to **25** by an additional three steps, and the details are described in the Supporting Information.

(18) (a) Hatakeyama, S.; Mori, H.; Kitano, K.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1994**, *35*, 4367. (b) Oishi, T.; Imaizumi, T.; Murata, M. *Chem. Lett.* **2010**, *39*, 108.

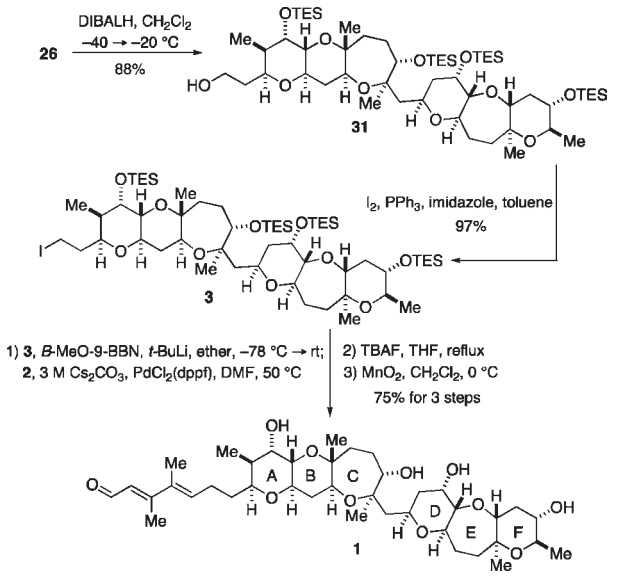
Scheme 5. Treatment of Tris-TES Ethers with DIBALH



had to be selectively removed in the presence of four secondary TES ethers.

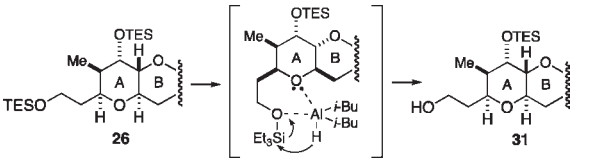
Recently we reported the highly selective deprotection of mono- and bis-silyl ethers by DIBALH.[19] This method was also applicable to the selective deprotection of a primary TES ether in the presence of two secondary TES ethers. Tris-TES ethers **27** and **28** were converted to the corresponding primary alcohols **29** and **30** in excellent yields (Scheme 5).

Scheme 6. Completion of the Total Synthesis



The completion of the total synthesis of **1** is illustrated in Scheme 6. Application of the above selective deprotection on pentakis-TES ether **26** gave primary alcohol **31** in 88% yield. Perhaps the neighboring ether oxygen atom of the A ring accelerated the deprotection and generated its high selectivity (Scheme 7). The primary alcohol **31** was converted to iodide **3** with I_2, PPh_3, and imidazole. Finally, connection of the fragments **2** and **3** by means of a Suzuki–Miyaura cross coupling[20] followed by the deprotection of all silyl groups and chemoselective oxidation of the allylic alcohol at C-1 gave rise to **1** in 75% yield for the three steps. The optical rotation and the other spectroscopic data of synthetic **1** were identical with those of natural **1**.

Scheme 7. Selective Deprotection of **26**



In conclusion, we have accomplished the first total synthesis of (−)-brevisin (**1**). The polycyclic ether core was constructed by means of a Suzuki–Miyaura cross coupling reaction and aldol addition as the key steps. It is noteworthy that the synthesis was accomplished in only 29 longest linear steps from commercially available 2-deoxy-D-ribose. Furthermore, based on our highly efficient synthetic strategy, we could synthesize over 70 mg of **1**. The present synthesis is a successful example of practically supplying a marine polycyclic ether compound and will be important for the elucidation of brevisin's biological activity.

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

(19) Kuranaga, T.; Ishihara, S.; Ohtani, N.; Satake, M.; Tachibana, K. *Tetrahedron Lett.* **2010**, *51*, 6345.
(20) Marshall, J.; Johns, B. *J. Org. Chem.* **1998**, *63*, 7885.