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Total Synthesis of (−)-Brevenal: A Concise Synthetic Entry to the Pentacyclic Polyether Core

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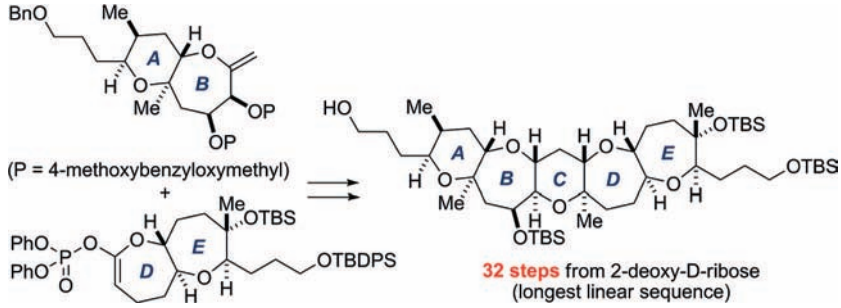
ABSTRACT



Total synthesis of (−)-brevenal, a novel marine polycyclic ether natural product, is described. Highly efficient and scalable entries to the AB-ring *exo*-olefin and the DE-ring enol phosphate and a rapid construction of the C-ring by means of our Suzuki-Miyaura coupling-based strategy realized a concise synthesis of the pentacyclic skeleton of (−)-brevenal. The present synthesis is considerably more efficient than our previous synthesis (longest linear sequence: 50 steps from 2-deoxy-D-ribose).

The structural complexity and intriguing biological activities of marine polycyclic ether natural products continue to attract the attention of chemists and biologists.[1,2] Brevenal, a novel member of this family of natural products, was isolated from the Florida red tide-forming dinoflagellate *Karenia brevis* by Baden and co-workers.[3] Its gross structure including the relative stereochemistry was disclosed as **1** based on extensive 2D-NMR analysis (Figure 1). We have recently reported the first total synthesis of (−)-brevenal, culminating in the structure revision of the originally proposed structure **1** and determination of the absolute configuration as shown by **2**.[4] The structural characteristic of this natural product is the densely functionalized pentacyclic polyether core arranged with a heavily substituted dienal side chain, which

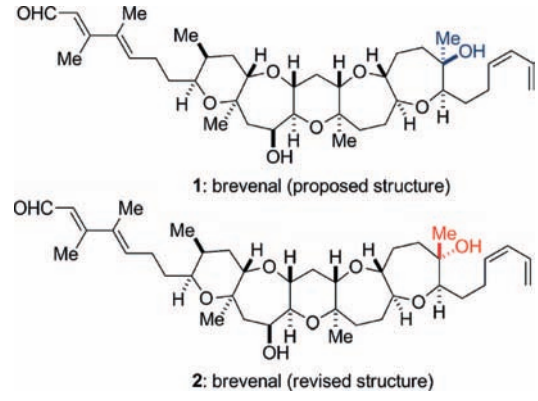


Figure 1. The proposed structure **1** and the revised structure **2** of (−)-brevenal.

(1) For reviews of marine polycyclic ether natural products, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev* **1993**, *93*, 1897. (b) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, 293. (c) Yasumoto, T. *Chem. Rec.* **2001**, *3*, 228.

(2) For recent reviews of the synthesis of marine polycyclic ether natural products, see: (a) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (b) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (c) Fuwa, H.; Sasaki, M. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 784.

(3) (a) Bourdelais, A. J.; Campbell, S.; Jacocks, H.; Naar, J.; Wright, J. L. C.; Carsi, J.; Baden, D. G. *Cell. Mol. Neurobiol.* **2004**, *24*, 553. (b) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M., Jr.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2.

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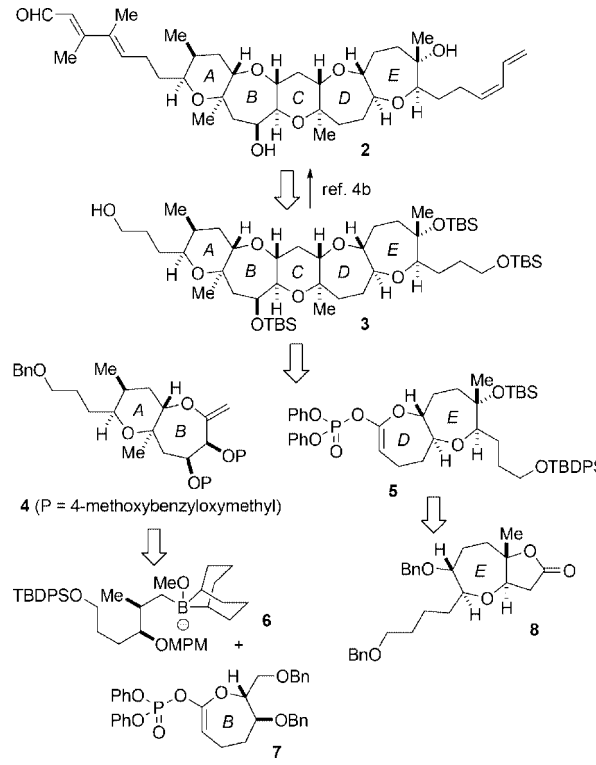
makes it a synthetically challenging molecule. Brevenal competitively displaces tritiated dihydrobrevetoxin B ([^{3}H]PbTx-3) from voltage-sensitive sodium channels (VSSCs) derived from rat brain synaptosomes in a dose dependent manner and antagonizes the toxic effects of brevetoxins *in vivo*. Even more importantly, Abraham, Baden, and co-workers have demonstrated that picomolar concentrations of brevenal effectively improves tracheal mucus clearance activity in an animal model of asthma.[5] Thus, brevenal represents a structurally novel source of therapeutic agents for treatment of mucociliary dysfunction associated with cystic fibrosis and other lung disorders. However, exploration of the structure-acitivity relationships of this natural product as well as elucidation of the mode of action on the molecular basis, including determination of the precise location of the brevenal-binding site on VSSCs, have yet to be investigated. In this context, the development of a focused library of structural analogues and designed multifunctional molecular probes would be necessary and, as a consequence, a concise and rapid access to the pentacyclic core structure of **2** becomes essential. Unfortunately, our first-generation synthesis of **2** suffered from the lengthy fragment syntheses and from the circuitous steps for assembly of these fragments, which were the serious bottlenecks for material throughput. Herein, we describe a total synthesis of **2** based on a concise synthetic entry to the pentacyclic polyether core. The synthesis features a 2-fold use of our Suzuki−Miyaura coupling/mixed thioacetalization strategy[6–8] to attain a high degree of convergency.

Our synthesis plan toward **2** is summarized in Scheme 1. We envisaged that pentacyclic core **3**, a key intermediate in the previous total synthesis,[4b] could be rapidly accessed from the AB-ring *exo*-olefin **4** and the DE-ring enol phosphate **5** by Suzuki−Miyaura coupling and subsequent construction of the C-ring by a mixed thioacetalization/methylation sequence. The AB-ring *exo*-olefin **4** was retrosynthetically divided into alkylborate **6** and the B-ring enol phosphate **7** based on a further application of the Suzuki−Miyaura coupling/mixed thioacetalization strategy. On the other hand, the DE-ring enol phosphate **5** was traced back to the E-ring **8** via lactonization of the D-ring. Thus, a 2-fold use of the Suzuki−Miyaura coupling/mixed thioacetalization strategy would realize a highly convergent synthesis of **2**.

The synthesis of the AB-ring *exo*-olefin **4** started with iodination of alcohol **9**,[4] which gave iodide **10** (Scheme 2).

Scheme 1. Synthesis Plan of (−)-Brevenal



Lithiation of **10** with *t*-BuLi in the presence of *B*-MeO-9-BBN generated an alkylborate,[9] which was coupled with enol phosphate **7**,[6b] corresponding to the B-ring of brevenal, to deliver enol ether **11** in 90% yield. Stereoselective hydroboration of **11** was best achieved using thexylborane, which was followed by oxidation[10] of the resultant alcohol to give ketone **12**. The stereochemistry at C11[11] was established by an NOE experiment as shown. Removal of the MPM group and subsequent treatment with EtSH/Zn(OTf)$_2$[12] afforded mixed thioacetal **13** in good yield. Introduction of the C12 angular methyl group was achieved by one-pot oxidation/methylation protocol,[12a] giving rise to bicycle **14** in 92% yield.

After removal of the benzyl groups, selective protection of the resultant primary alcohol as its TIPS ether led to alcohol **15**. To install the C14 hydroxy group, the C15 secondary alcohol of **15** was first regioselectively eliminated by a one-pot procedure.[13] Thus, treatment of **15** with Tf$_2$O/2,6-lutidine, followed by addition of DBU, afforded olefin

(4) (a) Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648. (b) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989.

(5) Abraham, W. M.; Bourdelais, A. J.; Sabater, J. R.; Ahmed, A.; Lee, T. A.; Serebriakov, I.; Baden, D. G. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 26.

(6) (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.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1851.

(7) (a) Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2981. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983. (c) Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294. (d) Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326.

(8) For reviews, see: (a) Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851. (b) Sasaki, M.; Fuwa, H. *Nat. Prod. Rep.* **2008**, *25*, 401.

(9) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751.

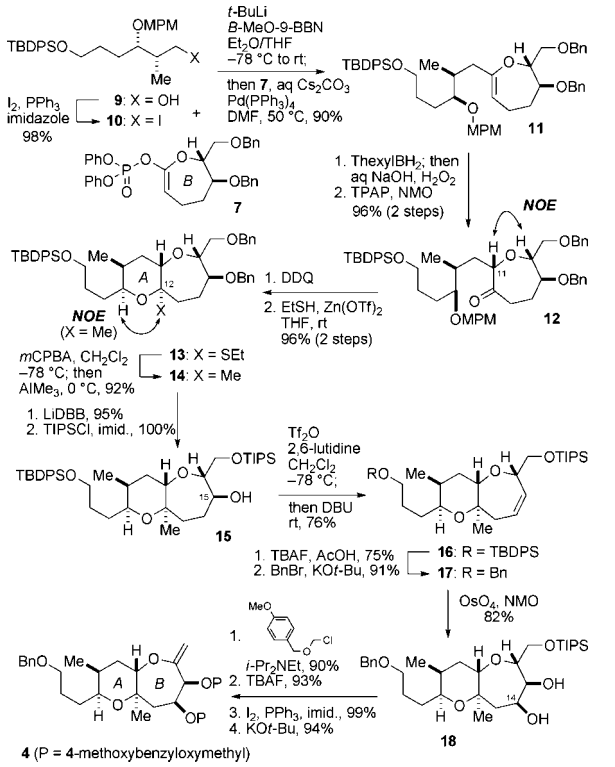
(10) Ley, S. V.; Normann, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(11) The carbon numbering in this paper corresponds to that of the natural product.

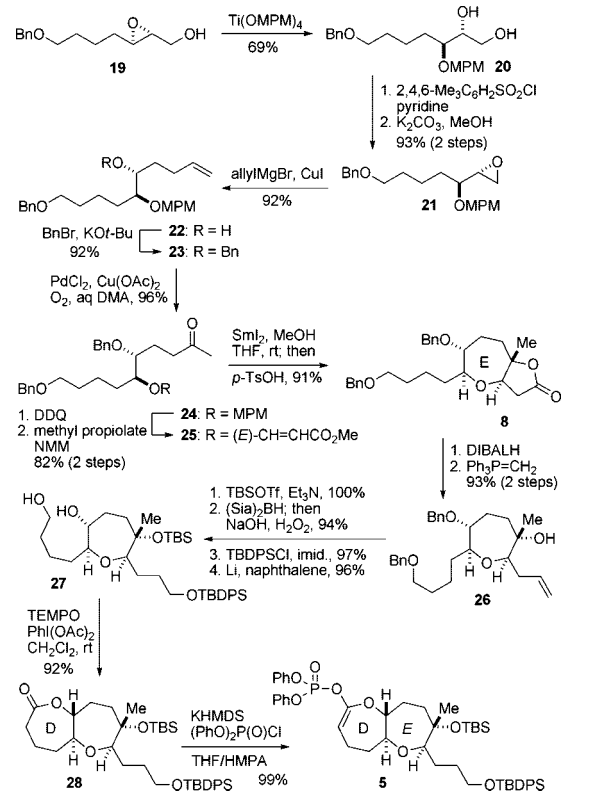
(12) (a) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371. (c) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019.

(13) We previously utilized a four-step sequence [(i) TPAP, NMO; (ii) LHMDS, TMSCl; (iii) OsO_4, NMO; (iv) DIBALH] to synthesize related diols. See ref 4 and: Sasaki, M.; Ebine, M.; Takagi, H.; Takakura, H.; Shida, T.; Satake, M.; Oshima, Y.; Igarashi, T.; Yasumoto, T. *Org. Lett.* **2004**, *6*, 1501.

Scheme 2. Synthesis of the AB-Ring *exo*-Olefin **4**



Scheme 3. Synthesis of the DE-Ring Enol Phosphate **5**



16 in 76% yield. After protective group manipulations, stereoselective dihydroxylation of the derived olefin **17** furnished diol **18** in 82% yield as a single stereoisomer. The stereochemical outcome of the present reaction was confirmed by an NOE experiment of the acetonide derivative of **18**.[14] Protection of **18** (4-methoxybenzyloxymethyl chloride, *i*-Pr_2NEt) and cleavage of the TIPS group gave an alcohol, which was iodinated and subsequently treated with KO*t*-Bu to furnish the AB-ring *exo*-olefin **4**.

The synthesis of the DE-ring enol phosphate **5** is summarized in Scheme 3. Regioselective opening of the known epoxide **19**,[15] readily available from 1,5-pentanediol in five steps, with $Ti(OMPM)_4$ provided diol **20** in good yield. Selective sulfonylation of the primary alcohol of **20** with 2,4,6-trimethylbenzenesulfonyl chloride/pyridine followed by base treatment gave epoxide **21**, which was then allylated with allylmagnesium bromide in the presence of CuI to afford alcohol **22**. Benzylation followed by Wacker oxidation[16] delivered methyl ketone **24**. Deprotection of the MPM group and subsequent attachment of an acrylate unit led to β-alkoxyacrylate **25**. Treatment of **25** with SmI_2 in the presence of MeOH (THF, room temperature)[17] furnished lactone **8** in 91% yield as a single stereoisomer. The stereochemistries of newly generated stereocenters were established by NOE experiments.[14] Reduction of **8** with DIBALH, followed by Wittig methylenation of the resultant hemiacetal, gave alcohol **26**. After conversion of **26** to **27** in four steps, direct oxidative cyclization of the 1,6-diol **27** using TEMPO/$PhI(OAc)_2$[18] furnished lactone **28** in a remarkably high yield. To the best of our knowledge, application of these conditions to oxidative cyclization of 1,6-diol to construct seven-membered lactone has not been reported. Enolization of **28** with KHMDS in the presence of $(PhO)_2P(O)Cl$ delivered the DE-ring enol phosphate **5**.

Assembly of the AB-ring *exo*-olefin **4** and the DE-ring enol phosphate **5** and subsequent construction of the C-ring were accomplished according to our Suzuki-Miyaura coupling-based strategy (Scheme 4). Thus, stereoselective hydroboration of **4** using 9-BBN-H generated an alkylborane, which was reacted with **5** in the presence of aqueous Cs_2CO_3 as a base and $Pd(PPh_3)_4$ as a catalyst to furnish enol ether **29** in 92% yield as a single stereoisomer. Hydroboration of **29** proceeded stereoselectively to give an alcohol, which was oxidized to give ketone **30** as a single stereoisomer. Cleavage of the 4-methoxybenzyloxymethyl and silyl groups,[19] mixed

(14) See Supporting Information for details.

(15) Liu, J.; Yang, J.-H.; Ko, C.; Hsung, R. P. *Tetrahedron Lett.* **2006**, *47*, 6121.

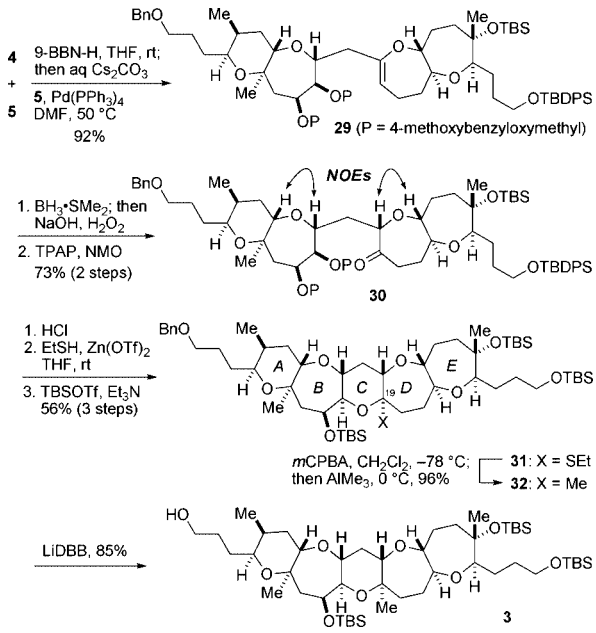
(16) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765.

(17) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099. (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859. (d) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853.

(18) For oxidation of 1,5-diols using TEMPO/$PhI(OAc)_2$, see: Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.

(19) Selective cleavage of the 4-methoxybenzyloxymethyl groups using DDQ, CAN, or Me_3SiBr gave unsatisfactory results.

Scheme 4. Total Synthesis of (−)-Brevenal



thioacetalization, and ensuing silylation of the resultant unprotected hydroxy groups delivered mixed thioacetal **31**. Introduction of the C19 methyl group was achieved in a one-pot manner (*m*CPBA; then $AlMe_3$), giving rise to the pentacyclic polyether **32** in 96% yield as a single stereoisomer. The stereochemistry of **32** was confirmed by a ROESY experiment. Finally, debenzylation of **32** using LiDBB[20] afforded alcohol **3**, whose spectroscopic properties are in full accordance with those of the authentic material that had been synthesized as an intermediate in our previous total synthesis of **2**.[4b] Thus, the present synthesis constitutes a formal total synthesis of **2**.

In summary, we have accomplished the total synthesis of (−)-brevenal based on a concise synthetic entry to the pentacyclic polyether core. The remarkable features of the present synthesis are: (1) a highly stereocontrolled, convergent synthesis of the AB-ring *exo*-olefin **4** by means of the Suzuki−Miyaura coupling/mixed thioacetalization strategy, (2) an efficient synthesis of the DE-ring enol phosphate **5** employing an oxidative lactonization of the D-ring, and (3) a rapid construction of the C-ring based on the second use of the Suzuki−Miyaura coupling-based strategy. The densely functionalized pentacyclic core structure **3** was successfully built up with a longest linear sequence (LLS) of just 32 steps. Thus, the present synthesis is considerably more efficient than our previous synthesis (LLS: 50 steps from 2-deoxy-D-ribose). The present synthesis should be effective for preparing diverse structural analogues and molecular probes for detailed investigations on the structure−activity relationships and the molecular mode of action of this biologically intriguing natural product. Further studies are currently underway along this line and will be reported in due course.

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Supporting Information Available: Stereochemical assignment of **8** and **18**, detailed experiemental procedures, spectroscopic data, and copies of ^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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