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Total Synthesis, Structure Revision, and Absolute Configuration of (–)-Brevenal

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Abstract

Total synthesis of structure **1** originally proposed for brevenal, a nontoxic polycyclic ether natural product isolated from the Florida red tide dinoflagellate, *Karenia brevis*, was accomplished. The key features of the synthesis involved (i) convergent assembly of the pentacyclic polyether skeleton based on our developed Suzuki–Miyaura coupling chemistry and (ii) stereoselective construction of the multi-substituted (*E,E*)-dienal side chain by using copper(I) thiophen-2-carboxylate (CuTC)-promoted modified Stille coupling. The disparity of NMR spectra between the synthetic material and the natural product required a revision of the proposed structure. Detailed spectroscopic comparison of synthetic **1** with natural brevenal, coupled with the postulated biosynthetic pathway for marine polyether natural products, suggested that the natural product was most likely represented by **2**, the C26 epimer of the proposed structure **1**. The revised structure was finally validated by completing the first total synthesis of (–)-**2**, which also unambiguously established the absolute configuration of the natural product.

Introduction

Marine polycyclic ether natural products continue to fascinate chemists and biologists because of their unique and highly complex molecular architecture coupled with diverse and extremely potent biological activities.^{1,2} Among these, brevetoxin-B, produced by the Florida red tide dinoflagellate, *Karenia brevis* (formerly known as *Gymnodinium breve* and *Ptychodiscus brevis*), is the first member of this class of natural products to be structurally elucidated by spectroscopic and X-ray crystallographic analysis by Nakanishi and co-workers in 1981 (Figure 1).³ Ever since, a number of congeners, including brevetoxin-A,⁴ have been isolated and structurally characterized. These toxic metabolites are known to exhibit their potent neurotoxicity by binding with a receptor site 5 on voltage-sensitive sodium channels (VSSC) in excitable membranes, thereby causing the channels to open at normal resting potentials with an increase in mean channel open time and inhibiting channel inactivation.⁵ Blooms of *K. brevis* have been associated with massive fish kills and marine mammal poisoning, and they are thought to be responsible for adverse human health effects, such as respiratory irritation and airway constriction observed in beach-goers during a red tide. In addition, the consumption

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Supporting Information Available: Full experimental details and spectroscopic data for all new compounds, comparison of ¹H and ¹³C NMR spectra for natural brevenal and synthetic **2**, and copies of ¹H and ¹³C NMR spectra for all new compounds (pdf). This material is available free of charge via the Internet at <http://pubs.acs.org>.

of shellfish contaminated with brevetoxins results in neurotoxic shellfish poisoning (NSP) in humans, which is characterized by sensory abnormalities, cranial nerve dysfunction, gastrointestinal symptoms, and sometimes respiratory failure.⁶ Hemibrevetoxin-B, another polycyclic ether compound, was isolated by Prasad and Shimizu from the same organism, and the molecular size is about one-half of that of brevetoxins.⁷ Hemibrevetoxin-B was reported to cause the same characteristic rounding of cultured mouse neuroblastoma cells as brevetoxins and show cytotoxicity at a concentration of 5 μ M.

Brevenal, isolated recently by Baden, Bourdelais, and co-workers from the laboratory cultures of *K. brevis* along with brevetoxins, represents the newest member of polycyclic ethers.⁸ The gross structure of brevenal, including the relative stereochemistry, was disclosed in 2004 as structure **1** on the basis of extensive 2D NMR studies; however, the absolute stereochemistry remained to be established. Although the size of the molecule is relatively compact compared with brevetoxins, the pentacyclic polyether core arranged with four methyl and two hydroxy groups and, especially, the characteristic heavily substituted left-hand (*E,E*)-dienal side chain make it a synthetically challenging target molecule. In addition, the biological profile of brevenal is particularly unique and intriguing in that it competitively displaces tritiated dihydrobrevetoxin-B (³H]-PbTx-3) from VSSC in rat brain synaptosomes in a dose-dependent manner and antagonizes the toxic effects of brevetoxins in vivo.^{8,9} More importantly, picomolar concentrations of brevenal increased tracheal mucus velocity to the same degree as that observed with millimolar concentrations of a sodium channel blocker, amiloride, which is used in the treatment of cystic fibrosis.¹⁰ Thus, brevenal represents a potential lead for the development of novel therapeutic agents for the treatment of mucociliary dysfunction associated with cystic fibrosis and other lung disorders.

The remarkable structural and biological aspects of this natural product led us to embark on its total synthesis. We have recently reported the first total synthesis of structure **1** originally proposed for brevenal by means of our developed Suzuki–Miyaura coupling-based convergent strategy.¹¹ However, the ¹H and ¹³C NMR spectra for the synthetic material were not identical to those reported for the natural product, suggesting that it is necessary to revise the initial structural assignment. Herein, we describe the details of our total synthesis of the proposed brevenal structure **1** and non-identity to the natural product. On the basis of the NMR distinctions, a revised structure **2**, the C26-epimer of **1**, was proposed and finally confirmed by the total synthesis of (–)-**2**, which has also led to unambiguous determination of the absolute configuration of the natural product.

Results and Discussion

Synthesis Plan

Our total synthesis of structure **1** originally proposed for brevenal was based on a retrosynthetic analysis as depicted in Scheme 1. The characteristic unsaturated side chains at both ends of the molecule were to be constructed at a late stage of the total synthesis. The right-hand (*Z*)-diene is the same as that found in the hemibrevetoxin-B structure, and thus this could be prepared by the precedented procedure, namely, selenyl–Wittig reaction using the ylide generated from phosphonium salt **4** followed by syn elimination of the selenoxide.¹² On the other hand, the left-hand side chain that contains a multi-substituted (*E,E*)-dienal moiety was planned to be constructed in a stereoselective manner by the Stille coupling of (*E*)-vinyl iodide **3** and (*E*)-vinyl stannane **5**.¹³ In turn, the pentacyclic polyether core in **3** was envisaged to be available from the AB ring enol phosphate **6** and the DE ring exocyclic enol ether **7** by means of our Suzuki–Miyaura coupling-based chemistry.^{14–16}

Synthesis of the AB Ring Fragment 6

The synthesis of the AB ring fragment **6** started with Evans aldol reaction of aldehyde **8** and oxazolidinone **9**, which provided the desired syn-aldol adduct (Scheme 2).¹⁷ The chiral auxiliary was reductively removed with NaBH₄¹⁸ to provide 1,3-diol **10** as a single stereoisomer in 90% overall yield. The resultant diol **10** was protected as the *p*-methoxybenzylidene acetal, which was then reduced with DIBALH in a regioselective manner to afford primary alcohol **11** in 94% yield for the two steps.¹⁹ Mesylation of **11** followed by displacement with sodium cyanide gave nitrile **12** in 96% yield (two steps). DIBALH reduction of the nitrile and subsequent Wittig reaction of the resulting aldehyde provided α,β -unsaturated ester **13** in 87% yield for the two steps. After reduction with DIBALH, Sharpless asymmetric epoxidation of the resultant allylic alcohol **14** under the stoichiometric conditions gave epoxy alcohol **15** in 88% yield. In contrast, under the catalytic conditions, the yield of **15** was moderate (ca. 50%) and several unidentified byproducts were formed. Oxidation of **15** followed by Wittig olefination provided vinyl epoxide **16** in 90% yield for the two steps. Upon exposure of **16** to DDQ (CH₂Cl₂/H₂O (20:1), room temperature), deprotection of the PMB group with concomitant 6-*endo* cyclization took place²⁰ to furnish the A ring pyran **17**, which was then protected as the TES ether **18** (89% yield for the two steps). The relative stereochemistry of **17** was established by NOE experiments as shown. Hydroboration of **18** with disiamylborane gave an alcohol (92% yield), which was then subjected to oxidation and Wittig reaction to afford α,β -unsaturated ester **19** in 86% yield for the two steps. Removal of the TES group under mild acidic conditions provided alcohol **20**. Hydrogenation of **20** with concomitant hydrogenolysis of the benzyl ester, followed by Yamaguchi lactonization,²¹ generated seven-membered lactone **21** (88% overall yield), which was then transformed to the requisite AB ring enol phosphate **6** by the usual method.²²

Synthesis of the DE Ring Fragment 7

For the synthesis of the DE ring fragment **7**, the known seven-membered ether **22**,²³ corresponding to the D ring, was selected as a starting material (Scheme 3). Benzylation of **22** followed by ozonolysis and reductive workup with NaBH₄ gave alcohol **23** in 96% yield for the two steps. The primary alcohol of **23** was protected as the benzyl ether and the benzylidene acetal was removed under acidic conditions to afford diol **24** in a quantitative yield for the two steps. Selective triflation of the primary alcohol followed by TBS protection of the residual secondary alcohol was carried out in one-pot following the method of Mori.²⁴ The resulting primary triflate was immediately subjected to nucleophilic displacement with allylmagnesium bromide in the presence of CuBr²⁵ to afford elongated olefin **25** in 85% overall yield. The terminal olefin of **25** was oxidatively cleaved (OsO₄, 4-methylmorpholine *N*-oxide (NMO); then NaIO₄) to give the corresponding aldehyde, which was treated with 1,3-propanedithiol in the presence of boron trifluoride etherate to provide alcohol **26** after deprotection of the silyl group (88% yield for the four steps). Hetero-Michael reaction of **26** with methyl propiolate and 4-methylmorpholine (NMM) followed by hydrolysis of the dithioacetal (MeI, NaHCO₃, aq MeCN) afforded β -alkoxyacrylate **27** in 99% yield for the two steps. Exposure of **27** to SmI₂ in the presence of methanol (THF, room temperature) effected reductive cyclization to form the seven-membered ether,²⁶ and after acidic treatment, tricyclic lactone **28** was obtained in 84% yield for the two steps as a single stereoisomer. DIBALH reduction of the γ -lactone and Wittig reaction of the resulting hemiacetal, followed by oxidation of the derived secondary alcohol with tetra-*n*-propylammonium perruthenate (TPAP)/NMO,²⁷ led to ketone **29** in 91% yield for the three steps. At this stage, the stereochemistry at the C27 position²⁸ was confirmed by NOE experiment as shown.

We next investigated stereoselective methylation of ketone **29** using several nucleophiles under various conditions, and the results are summarized in Table 1. Treatment of **29** with excess trimethylaluminum in CH₂Cl₂ produced an approximately 1.3:1 mixture of tertiary alcohols

30a and **30b** along with recovered starting material **29** (entry 1). Exposure of **29** to excess methylmagnesium bromide in THF at $-78\text{ }^{\circ}\text{C}$ gave a mixture of **30a** and **30b** with slightly improved diastereoselectivity (ca. 2.5:1 dr), but a significant amount of ketone **29** was recovered (entry 2). Increasing the reaction temperature dramatically improved the conversion yield without affecting the diastereoselectivity. Thus, treatment of **29** with 1.5 equiv of methylmagnesium bromide in THF at $-78\text{ }^{\circ}\text{C}$ to room temperature provided **30a,b** in 99% combined yield (ca. 2.3:1 dr, entry 3). The use of toluene as the solvent led to less favorable ratio (ca. 1:1.3 dr) of products (entry 4). Finally, it was found that addition of methyllithium (1.2 equiv) to **29** in THF at $-78\text{ }^{\circ}\text{C}$ followed by gradual warming to room temperature furnished a 10:1 mixture of **30a** and **30b** in 97% yield (entry 5). The undesired minor isomer **30b** could be easily separated by flash chromatography. Stereochemistry at the C26 tertiary stereocenter of **30a** was unequivocally established by NOE between 26-Me and 27-H. The corresponding NOE was not observed for the isomer **30b**.

Conversion of tertiary alcohol **30a** to the DE ring fragment **7** was carried out as illustrated in Scheme 4. Thus, **30a** was protected with TBSOTf and triethylamine to give the TBS ether **31**. Hydroboration of the terminal olefin and removal of the benzyl groups under hydrogenolysis, followed by *p*-methoxy-benzylidene acetal formation, led to primary alcohol **32** in 80% yield for the three steps. Benzylation followed by reductive cleavage of the acetal with DIBALH provided alcohol **33** (85% yield, two steps). Finally, iodination and subsequent base treatment furnished the DE ring exo-olefin fragment **7** in 99% yield for the two steps.

Construction of the Pentacyclic Polyether Core

With the requisite fragments in hand, we set out to assemble the pentacyclic polyether core as summarized in Schemes 5 and 6. Hydroboration of the DE ring exocyclic enol ether **7** with 9-BBN produced the corresponding alkylborane, which was in situ reacted with the AB ring enol phosphate **6** in the presence of aqueous Cs_2CO_3 and $\text{Pd}(\text{PPh}_3)_4$ in DMF at $50\text{ }^{\circ}\text{C}$ to furnish the desired coupling product **34** as a single stereoisomer (Scheme 5). The endocyclic enol ether within **34** was then hydroborated with $\text{BH}_3\text{-SMe}_2$ to give alcohol **35** (84% overall yield from **7**), which was oxidized with TPAP/NMO to afford ketone **36** in 98% yield. At this stage, the newly generated stereocenters at C16 and C18 were unambiguously confirmed by NOE experiments as shown. Subsequent stereoselective introduction of the C14 hydroxy group was successfully achieved by the previously described method.^{16c,d,29} Thus, treatment of ketone **36** with LiHMDS in the presence of TMSCl and triethylamine gave the corresponding silyl enol ether, which was then treated with OsO_4/NMO to provide α -hydroxy ketone **37** as the sole product (87% for the two steps).

Subsequent reduction of hydroxy ketone **37** with DIBALH in THF at $-78\text{ }^{\circ}\text{C}$ provided an approximately 10:1 mixture of *cis*-diol **38** and its *trans*-isomer in 83% combined yield, along with a 12% yield of recovered **37** (Scheme 6). The desired isomer **38** could be easily separated by flash chromatography. The newly generated stereocenters at the C14 and C15 positions were established by derivatization to the cyclopentylidene acetal **39** and NOE experiments (Figure 2). It is noteworthy that DIBALH reduction of the TES-protected derivative of **37** led exclusively to the corresponding α -alcohol, suggesting the importance of the free hydroxy group. The outcome of this stereoselective reduction of **37** can be explained as follows. Initially, the C14 hydroxy group reacts with DIBALH to form the corresponding aluminum alkoxide, which coordinates to the adjacent C15 carbonyl group to form a five-membered chelate structure, thereby blocking the β -side of the molecule and forcing the second equivalent of the reductant to approach from the less hindered α -side.

After protection of **38** as the bis-TES ether, oxidative removal of the PMB group with DDQ, followed by oxidation of the resulting secondary alcohol with TPAP/NMO, led to ketone **40** in 88% yield for the three steps. To complete the C ring with an angular methyl group at C19,

ketone **40** was treated with ethanethiol in the presence of zinc triflate in THF at room temperature to effect deprotection of the TES groups with concomitant formation of a mixed thioacetal to generate **41** in 79% yield.³⁰ After protection of the secondary hydroxy group as the TBS ether (97%), introduction of the C19 axial methyl group was next investigated. Although we initially attempted oxidation of the sulfur within **42** with *m*CPBA to the corresponding sulfone under various conditions, it became evident that the mixed sulfonyl acetal derived from **42** was so prone to undergo hydrolysis that we could only obtain the corresponding hemiacetal derivative. Therefore, we decided to avoid isolation of the unstable intermediate and carry out the oxidation–methylation in a one-pot manner.^{30a} Thus, after oxidation of **42** with *m*CPBA at $-78\text{ }^{\circ}\text{C}$, excess amount of trimethylaluminum (3×4 equiv + 2 equiv) was added and the resulting mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$. Gratifyingly, this one-pot procedure ensured the desired pentacyclic polyether core **43** in 92% yield as a single isomer. The addition of trimethylaluminum in several portions was crucial for the success of the present process. The newly generated stereocenters were unambiguously established on the basis of NOE studies and $^3J_{\text{H,H}}$ data (Figure 3).

Model Experiments for the Synthesis of the Multi-Substituted (*E,E*)-Diene Side Chain

Having constructed the pentacyclic polyether skeleton, we next turned our attention to construction of the left-hand side chain. The multi-substituted (*E,E*)-dienal side chain is one of the characteristic structural features of brevenal. Although a survey of the literature suggested the difficulty of constructing such a heavily substituted diene system by means of palladium(0)-catalyzed cross-coupling reactions,¹³ we planned to utilize Stille coupling for connecting the C3–C4 bond. We first set out on model experiments in order to explore optimal conditions. (*E*)-Vinyl stannane **5** and (*E*)-vinyl iodide **44** (*E:Z* = ca. 4:1) were chosen as model substrates (Table 2). Stille coupling of **5a** and **44** under the conventional conditions led to only a trace amount of the desired diene **45a**, and significant amounts of the starting materials were recovered (entry 1). We assumed that this disappointing result was attributable to the low reactivity of **5a** and **44** arising from steric hindrance. We reasoned that use of a soft ligand such as (2-furyl)₃P or Ph₃As, which accelerates the transmetalation step of the catalytic cycle of Stille coupling,³¹ and copper(I) salt as a co-catalyst, which promotes transmetalation of vinyl stannane **5** to a more reactive copper species,³² would be favorable in the present case. In the event, under the influence of the Pd₂(dba)₃/(2-furyl)₃P/CuI or Pd₂(dba)₃/Ph₃As/CuI catalyst system, Stille coupling of a sterically less encumbered vinyl stannane **5b** and **44** proved to be very effective, giving diene **45b** in acceptable yields (entries 2 and 3). However, increasing the reaction temperature to $60\text{ }^{\circ}\text{C}$ caused significant isomerization of the diene configuration (entries 4 and 5). The structure of the isomerized byproduct, (*E,Z*)-diene **46**, was confirmed by NOE experiments. Gratifyingly, it was found that the use of copper(I) thiophene-2-carboxylate (CuTC)³³ instead of CuI realized further improvement of the yield of **45b** (84% yield, entry 6). When the TBDPS-protected **5a** was again used as a coupling partner, homocoupling product **47** was formed as a byproduct and hence the yield of the desired **45a** was slightly lowered (entries 7 and 8).

Total Synthesis of the Proposed Structure of Brevenal

Having secured the reliable reaction conditions for constructing the left-hand side chain, the final stage of the total synthesis of **1** was executed as shown in Scheme 7. Reductive removal of the benzyl group from **43** with LiDBB³⁴ was followed by reprotection as the TBS group to give silyl ether **48**. Selective removal of the primary TBDPS group from **48** in the presence of the three TBS groups was successfully carried out according to the procedure of Nakata and co-workers,³⁵ leading to primary alcohol **49** in 73% yield after three recycles.³⁶ Oxidation of **49** with Dess–Martin periodinane³⁷ followed by treatment of the resulting aldehyde with the Ohira–Bestmann reagent (K₂CO₃, MeOH)³⁸ produced an alkyne, which was then methylated with *n*-butyllithium/methyl iodide to provide alkyne **50** in excellent overall yield. At this stage,

the robust TBS protecting groups were replaced with the easily removable TES ethers. Thus, alkyne **50** was treated with HF•pyridine, and the resulting triol was reprotected with TESOTf and triethylamine to give tris-TES ether **51**. Regioselective silylcupration of **51** with $(\text{Me}_2\text{PhSi})_2\text{Cu}(\text{CN})\text{Li}_2$ ³⁹ delivered the desired vinylsilane **52** in an approximately 9:1 regioselectivity. The regiochemistry of **52** was confirmed by the characteristic pattern of the olefinic proton (dd, $J = 7.0, 7.0$ Hz). Conversion of **52** to vinyl iodide **3**, required for the projected Stille coupling, was performed on exposure to *N*-iodosuccinimide (NIS) in MeCN/THF (4:1) at room temperature.⁴⁰ Under these reaction conditions, isomerization of the olefin stereochemistry partially occurred and ca. 6:1 mixture of (*E*)-vinyl iodide **3** and its (*Z*)-isomer, along with small amounts of regioisomers, were produced in 99% combined yield from **51**. The (*E*)-geometry of **3** was tentatively assigned because it is well-known that the iododesilylation generally proceeds with retention of configuration,⁴⁰ and this was later confirmed by characterization of the cross-coupled product **53** (vide infra). Without separation of these isomers, the crucial Stille coupling was carried out under the established conditions. Thus, cross-coupling of **3** with vinyl stannane **5b** in the presence of the $\text{Pd}_2(\text{dba})_3/\text{Ph}_3\text{As}/\text{CuTC}$ catalyst system in THF/DMSO (1:1) at room temperature proceeded smoothly to furnish (*E,E*)-diene **53** in 63% yield as a single stereoisomer, after purification by flash chromatography.⁴¹ The stereochemistry of the diene system was unequivocally established by NOE experiments as shown.

After protection of the allylic alcohol of **53** as the TBDPS ether, the primary TES ether was selectively removed with PPTS to give alcohol **54** in 74% yield for the two steps. Introduction of the right-hand (*Z*)-diene side chain was performed without incident according to the procedure of Nicolaou et al.¹² Thus, oxidation of **54** with $\text{SO}_3\cdot\text{pyridine}/\text{DMSO}$ followed by Wittig olefination using the ylide, derived from phosphonium salt **4**, and subsequent hydrogen peroxide treatment led to conjugated (*Z*)-diene **55** in 75% overall yield from **54**. Global deprotection of the silyl protecting groups from **55** by the action of TAS-F⁴² provided triol **56** in 79% yield. Finally, chemoselective oxidation of the C1 alcohol by MnO_2 completed the synthesis of the proposed structure **1** for brevenal in a quantitative yield.

Revised Structure of Brevenal

Unfortunately, however, the ¹H and ¹³C NMR spectra of synthetic **1** were not identical with those of the authentic sample, suggesting that revision of the originally proposed structure of brevenal is necessary (Figure 4). For detailed comparison with the natural product, the ¹H and ¹³C NMR data of synthetic **1** were carefully assigned on the basis of extensive 2D NMR experiments, and the results are summarized in Tables 3 and 4 and Figure 5. The ¹H and ¹³C NMR chemical shifts in the left-hand region of synthetic **1** matched very closely those reported for the natural brevenal. In contrast, there were subtly distinct discrepancies of the chemical shifts in the DE ring region. Particularly, the observed chemical shifts around the C26 tertiary alcohol of **1** significantly deviated from those for the natural product, suggesting that an error (s) may exist somewhere around the E ring. COSY, HSQC, and HMBC correlations of the synthetic sample completely reproduced those of the authentic sample. However, a series of intense cross-peaks were observed between 26-Me/27-H and 26-Me/28-H₂ in the NOESY spectrum of synthetic **1** (Figure 5), whereas no such NOESY correlations have been reported for naturally occurring brevenal.^{8b} These NMR variations prompted us to propose the stereochemical inversion of the C26 tertiary alcohol within **1**, giving the revised structure **2** for brevenal.

The revised structure **2** is also supported by the postulated biosynthetic pathway for ladder-shaped polycyclic ether marine natural products (i.e., a cascade of polyepoxide cyclization) proposed by Shimizu and Nakanishi, independently (Figure 6).^{7,43,44} The stereochemistry at

C26 of brevenal would be epimeric to the proposed structure **1**, provided that a similar biosynthetic route is applicable to brevenal (Figure 6).

Total Synthesis of Revised Structure and the Absolute Configuration of Brevenal

To confirm our postulated idea, we turned to the synthesis of the C26 epimer **2** of the originally proposed structure **1**. Starting with an intermediate **25** in the synthesis of **7** (see Scheme 3), the requisite DE ring fragment **57** (26-*epi*-**7**) was prepared as summarized in Scheme 8. Wacker–Tsuji reaction⁴⁵ of the terminal olefin within **25** using the PdCl₂/Cu(OAc)₂ system⁴⁶ provided methyl ketone **58** in 92% yield. Removal of the TBS group from **58** followed by incorporation of a β -alkoxyacrylate unit to the resulting secondary alcohol produced **59** in high overall yield. Reductive cyclization of **59** with SmI₂ (MeOH/THF, room temperature) proceeded smoothly to form the seven-membered ether ring with the desired stereochemistry at C26, providing a mixture of γ -lactone **60** and hydroxy ester **61** in 57% and 37% yield, respectively.²⁶ The C26 and C27 stereochemistries of **60** were confirmed by NOE experiments as shown. Each of these compounds was cleanly reduced with lithium aluminum hydride (THF, 0 °C) to yield the same diol **62** in high yield. After protection as the bis-TBS ether, selective cleavage of the primary TBS ether under acidic conditions provided alcohol **63** in 90% yield for the two steps. Oxidation with SO₃•pyridine/DMSO followed by Wittig methylenation of the resulting aldehyde led to **64** (94% yield, two steps), which was subsequently transformed to the DE ring fragment **57** following a similar sequence described for the conversion of **31** to **7** (see, Scheme 4).

Convergent union of the DE ring fragment **57** and the AB ring enol phosphate **6** and subsequent elaboration of the resulting cross-coupled product **67** could be performed in much the same way as that used to reach **1** and proceeded in similar yields, thus completing the total synthesis of the revised structure **2** for brevenal (Scheme 9). To our delight, the ¹H and ¹³C NMR spectra and high-resolution mass spectrum of synthetic **2** were completely identical with those of the natural product, culminating in a conclusion that the C26 epimer of the originally proposed structure is the correct structure of brevenal. In addition, synthetic brevenal **2** exhibited specific rotation, $[\alpha]_D^{27} -33.5$ (*c* 0.27, benzene), which matched the value $[\alpha]_D^{27} -32.3$ (*c* 0.27, benzene) for the natural product; thus, the absolute configuration of brevenal was unequivocally determined to be shown as structure **2**.

Conclusion

We accomplished the first total synthesis of the proposed structure **1** of brevenal. The key features of our synthesis include a convergent assembly of the pentacyclic polyether skeleton by using the Suzuki–Miyaura coupling-based strategy and a stereoselective construction of the left-hand multi-substituted (*E,E*)-diene system by the CuTC-promoted modified Stille coupling. The ¹H and ¹³C NMR spectra of synthetic **1** did not match those for the natural product. Detailed NMR comparison of the synthetic material with the natural substance and the proposed biosynthesis of ladder-shaped polycyclic ether natural products led us to propose a revised structure **2**, the C26-epimer of **1**. In the event, the revised structure was validated through total synthesis, which also led to determination of the absolute configuration. This study demonstrates the important role of stereoselective total synthesis in structure determination of complex natural products.⁴⁷ Moreover, the highly convergent nature of the present synthesis will allow divergent total synthesis of structural analogues for more detailed structure–activity relationship studies of this intriguing natural product. Further studies along this line are currently underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

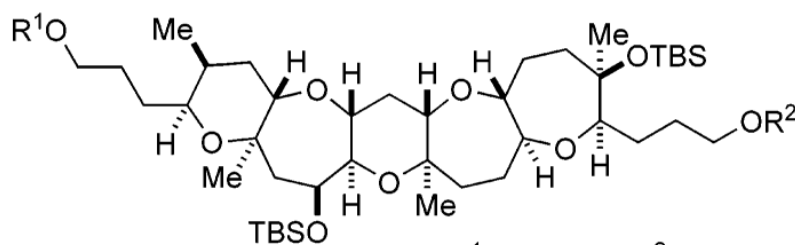
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36. The reaction mixture was stirred at room temperature overnight (ca. 13 h). Since, at this point, ca. 50% of the starting material **48** remained unreacted and a small amount of diol **S8** was observed by TLC analysis, the reaction was quenched. After separation of **48**, **49**, **S8**, and **S7** by flash chromatography, recycling of the recovered **48** (three times) provided **49** (78%), **S8** (8%) and **S7** (12%).



48: R¹ = TBDPS, R² = TBS

49: R¹ = H, R² = TBS

S8: R¹ = R² = H

S7: R¹ = TBDPS, R² = H

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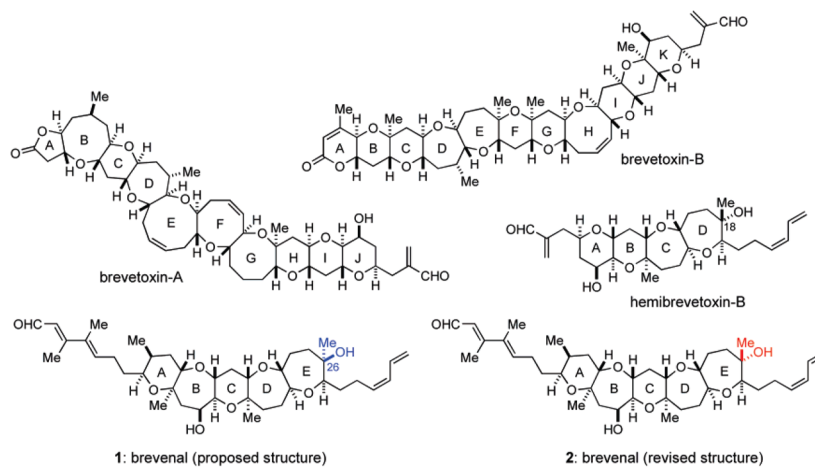
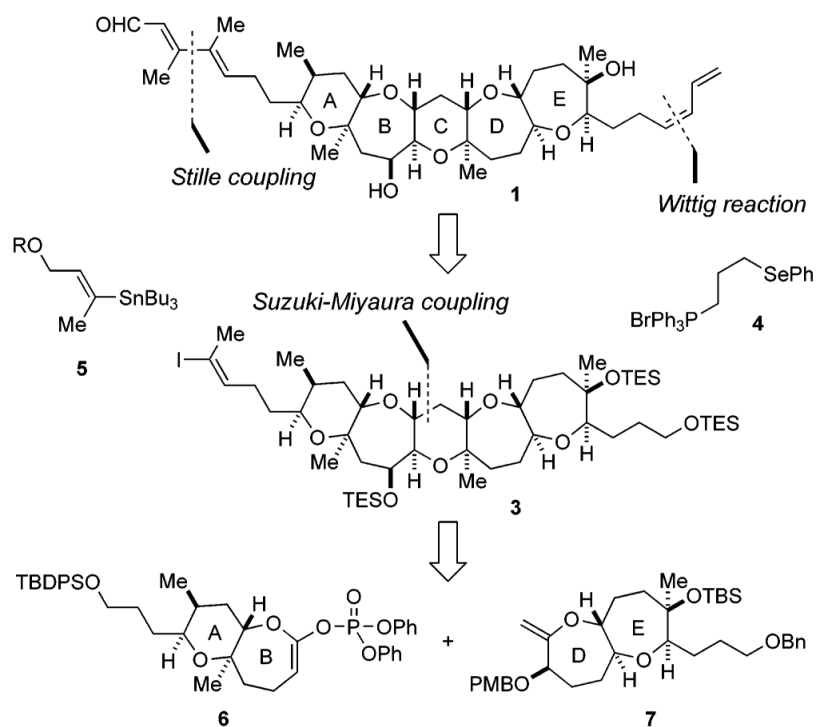
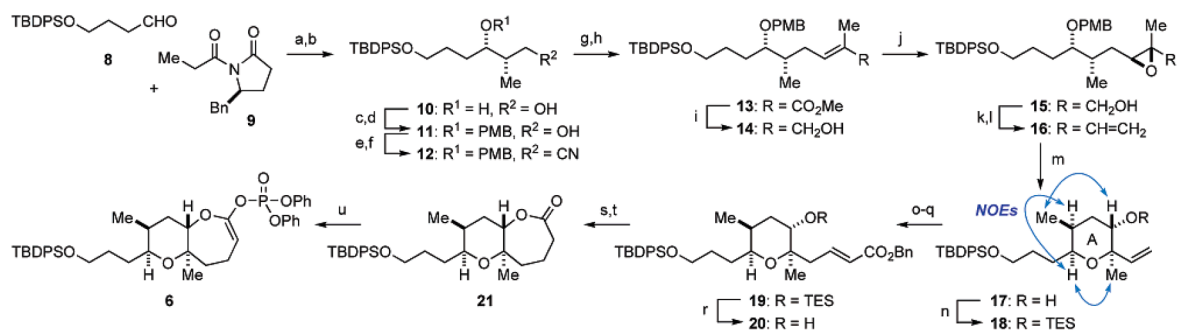


Figure 1. Structures of brevetoxin-A, brevetoxin-B, hemibrevetoxin-B, and brevenal (proposed structure 1 and revised structure 2).



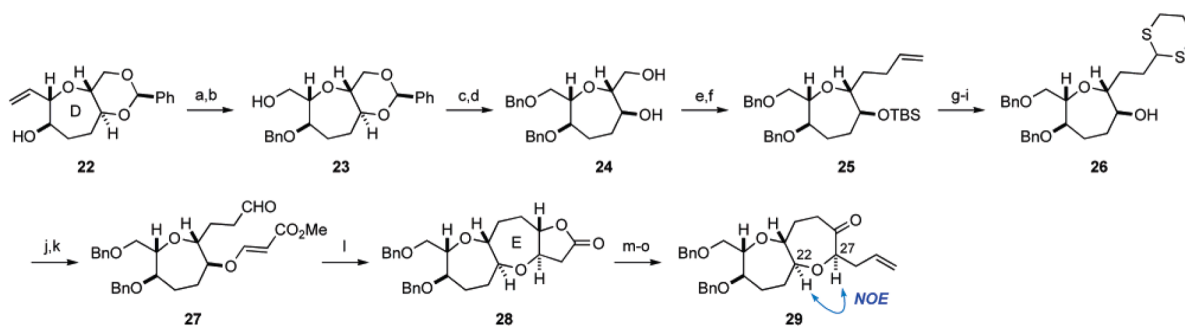
Scheme 1.
Retrosynthetic Analysis



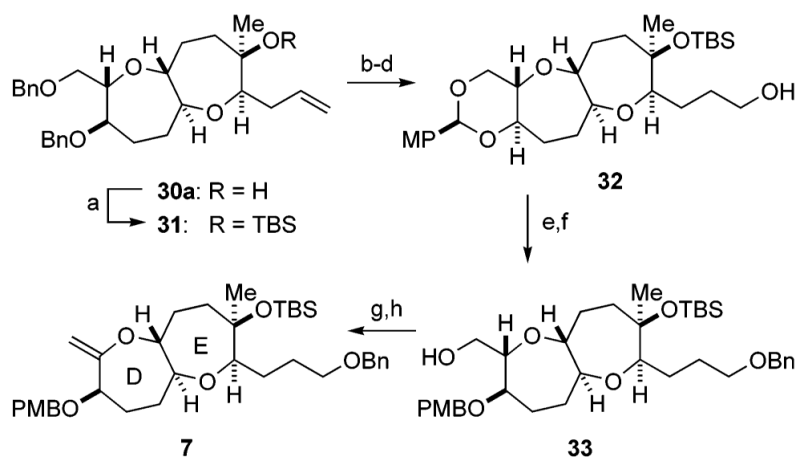
Scheme 2.

Synthesis of the AB Ring Fragment^a

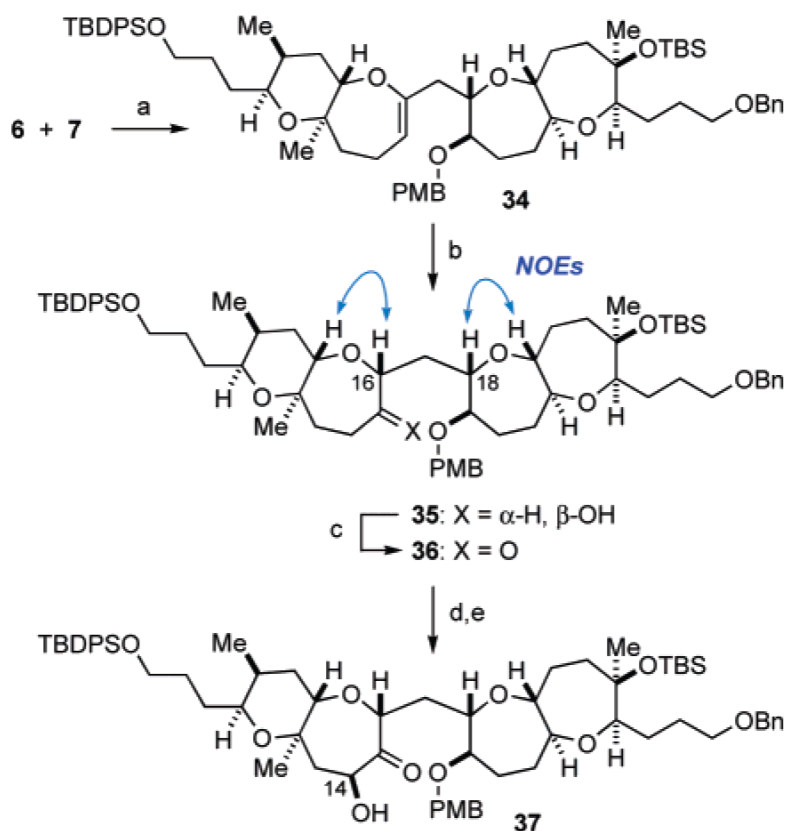
^a Reagents and conditions: (a) *n*-Bu₂BOTf, Et₃N, CH₂Cl₂, -78 → 0 °C; (b) NaBH₄, THF/H₂O, rt, 90% (two steps); (c) *p*-MeOC₆H₄CH(OMe)₂, PPTS, CH₂Cl₂, rt; (d) DIBALH, CH₂Cl₂, -78 → -40 °C, 94% (two steps); (e) MsCl, Et₃N, CH₂Cl₂, 0 °C; (f) NaCN, DMSO, 60 °C, 96% (two steps); (g) DIBALH, CH₂Cl₂, -78 °C, 90%; (h) Ph₃P=C(Me)CO₂Et, toluene, 100 °C, 97%; (i) DIBALH, CH₂Cl₂, -78 °C, quant.; (j) (+)-DET, Ti(O*i*-Pr)₄, *t*-BuOOH, CH₂Cl₂, -40 °C, 88%; (k) SO₃•pyridine, Et₃N, DMSO/CH₂Cl₂ (1:1), 0 °C; (l) Ph₃P⁺CH₃Br⁻, NaHMDS, THF, 0 °C, 90% (two steps); (m) DDQ, CH₂Cl₂/H₂O (20:1), rt; (n) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 89% (two steps); (o) (Sia)₂BH, THF, 0 °C; then aq NaHCO₃, 30% H₂O₂, rt, 92%; (p) SO₃•pyridine, Et₃N, DMSO/CH₂Cl₂ (1:1), 0 °C; (q) Ph₃P=CHCO₂Bn, toluene, 60 °C, 86% (two steps); (r) 1 M HCl, THF, rt, 95%; (s) H₂, 20% Pd(OH)₂/C, THF/MeOH (2:1), rt, 90%; (t) 2,4,6-Cl₃C₆H₂COCl, Et₃N, THF, 0 °C → rt; then DMAP, toluene, 110 °C, 98%; (u) KHMDS, (PhO)₂P(O)Cl, HMPA, THF, -78 °C, 96%.

**Scheme 3.****Synthesis of Ketone 29^a**

^a Reagents and conditions: (a) *KOt*-Bu, BnBr, *n*-Bu₄NI, THF, rt; (b) O₃, CH₂Cl₂/MeOH (1:1), -78 °C; then NaBH₄, 0 °C, 96% (two steps); (c) NaH, BnBr, THF/DMF (1:1), rt; (d) CSA, MeOH/CH₂Cl₂ (10:1), rt, quant. (two steps); (e) Tf₂O, 2,6-lutidine, CH₂Cl₂, -78 °C; then TBSOTf, 0 °C; (f) allylMgBr, CuBr, Et₂O, 0 °C, 85% (two steps); (g) OsO₄, NMO, THF/H₂O (7:1), rt; then NaIO₄, rt; (h) HS(CH₂)₃SH, BF₃·OEt₂, CH₂Cl₂, -78 → 0 °C; (i) TBAF, THF, rt, 88% (three steps); (j) methyl propiolate, NMM, CH₂Cl₂, rt; (k) MeI, NaHCO₃, MeCN/H₂O (4:1), rt, 99% (two steps); (l) SmI₂, MeOH, THF, rt; then *p*-TsOH·H₂O, toluene, 80 °C, 84% (two steps); (m) DIBALH, CH₂Cl₂, -78 °C; (n) Ph₃P⁺CH₃Br⁻, NaHMDS, THF, 0 °C → rt, 94% (two steps); (o) TPAP, NMO, 4 Å molecular sieves, CH₂Cl₂, rt, 97%.

**Scheme 4.****Synthesis of the DE Ring Fragment 7^a**

^a Reagents and conditions: (a) TBSOTf, Et₃N, CH₂Cl₂, rt, quant.; (b) 9-BBN, THF, rt; then aq NaHCO₃, 30% H₂O₂, rt; (c) H₂, 20% Pd(OH)₂/C, MeOH, rt; (d) *p*-MeOC₆H₄CH(OMe)₂, PPTS, CH₂Cl₂, rt, 70% (three steps); (e) KO^{*t*}-Bu, BnBr, *n*-Bu₄NI, THF, rt; (f) DIBALH, CH₂Cl₂, -78 → 0 °C, 87% (two steps); (g) I₂, PPh₃, imidazole, benzene, rt; (h) KO^{*t*}-Bu, THF, 0 °C, 92% (two steps).

**Scheme 5.**Synthesis of α -Hydroxy Ketone **37**^a

^a Reagents and conditions: (a) **7**, 9-BBN, THF, rt; aq Cs_2CO_3 , **6**, $\text{Pd}(\text{PPh}_3)_4$, DMF, 50 °C; (b) $\text{BH}_3 \cdot \text{SMe}_2$, THF, rt; then aq NaHCO_3 , 30% H_2O_2 , rt, 84% (two steps); (c) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2 , 0 °C, 98%; (d) LiHMDS , TMSCl , Et_3N , THF, -78 °C; (e) OsO_4 , NMO, THF/ H_2O (4:1), rt, 87% (two steps).

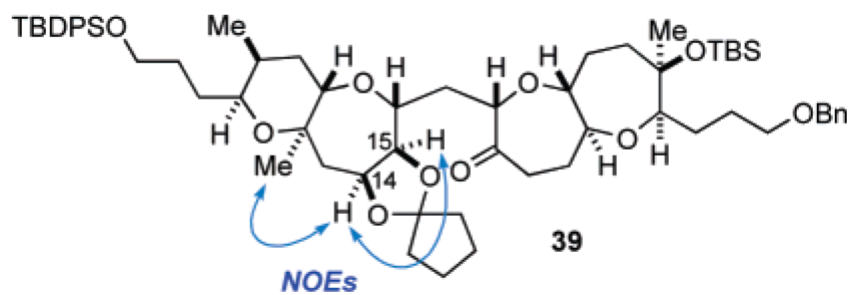


Figure 2.
Stereochemical confirmation of *cis*-diol **38**.

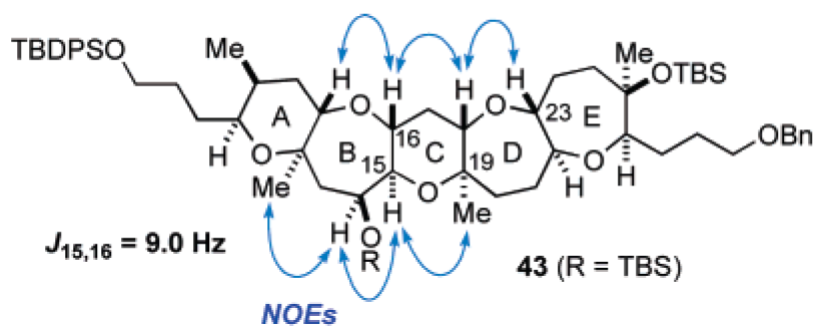
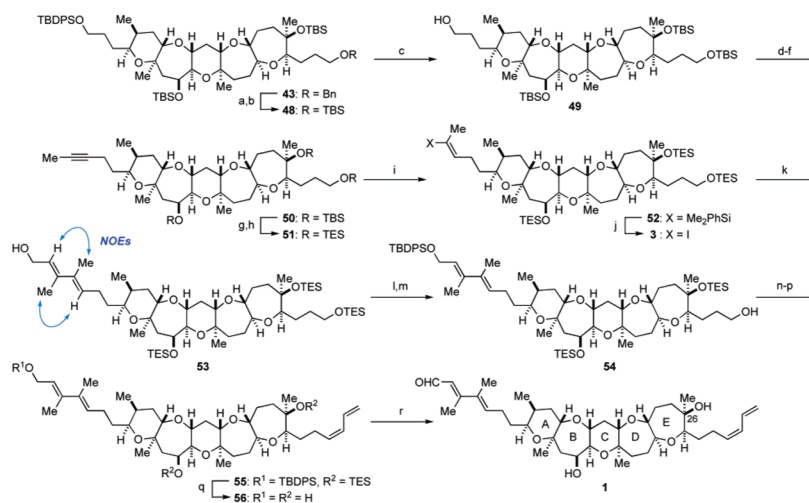


Figure 3.
Stereochemical confirmation of pentacyclic polyether **43**.



Scheme 7.

Total Synthesis of the Proposed Structure **1** for Brevenal^a

^a Reagents and conditions: (a) LiDBB, THF, $-78\text{ }^{\circ}\text{C}$, 99%; (b) TBSOTf, Et₃N, CH₂Cl₂, $0\text{ }^{\circ}\text{C}$, 98%; (c) TBAF, AcOH, THF, rt, 78% after three recycles; (d) Dess-Martin periodinane, CH₂Cl₂, rt; (e) Bestmann reagent, K₂CO₃, MeOH, rt; (f) *n*-BuLi, THF/HMPA (10:1), $-78\text{ }^{\circ}\text{C}$; then MeI, rt, 99% (three steps); (g) HF•pyridine, THF, rt, 96%; (h) TESOTf, Et₃N, CH₂Cl₂, $0\text{ }^{\circ}\text{C}$, 99%; (i) (Me₂PhSi)₂Cu(CN)Li₂, THF, $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, regioselectivity = ca. 9:1; (j) NIS, MeCN/THF (3:1), rt, 99% (two steps), *E:Z* = 6:1; (k) **5b**, Pd₂(dba)₃, Ph₃As, CuTC, DMSO/THF (1:1), rt, 63%; (l) TBDPSCl, imidazole, DMF, $0\text{ }^{\circ}\text{C}$, 99%; (m) PPTS, CH₂Cl₂/MeOH (4:1), $0\text{ }^{\circ}\text{C}$, 75%; (n) SO₃•pyridine, Et₃N, CH₂Cl₂/DMSO (3:1), $0\text{ }^{\circ}\text{C}$; (o) **4**, *n*-BuLi, HMPA, THF, $-78\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 97% (two steps); (p) 30% H₂O₂, NaHCO₃, THF, rt, 77%; (q) TASF, THF/DMF (1:1), rt, 79%; (r) MnO₂, CH₂Cl₂, rt, quant.

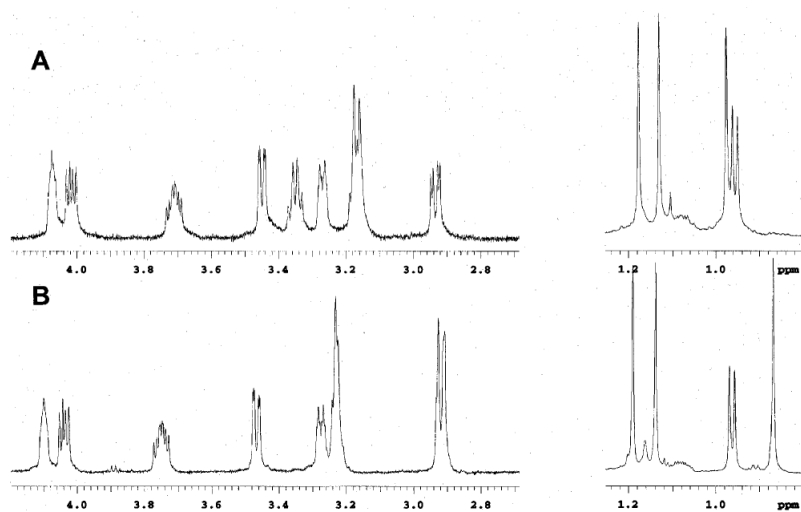


Figure 4. Partial ^1H NMR spectra (600 MHz, C_6D_6) of the natural brevenal (panel A) and synthetic **1** (panel B).

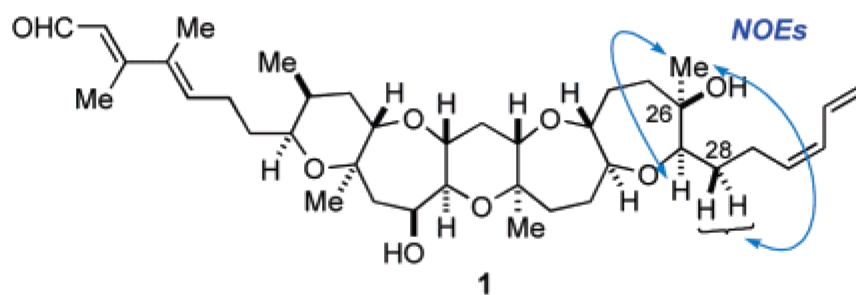


Figure 5.
Selected key NOE data for synthetic **1**.

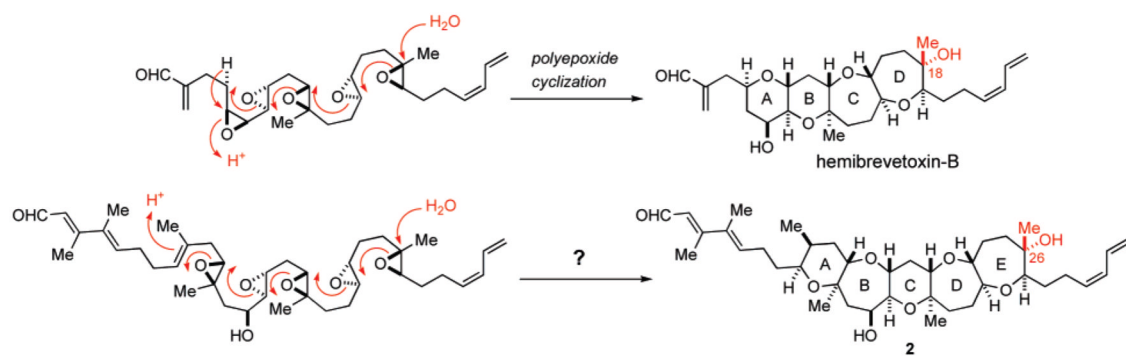
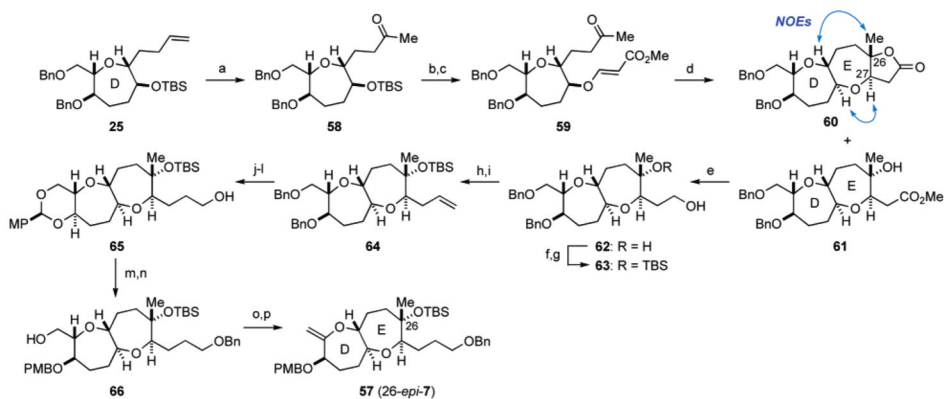
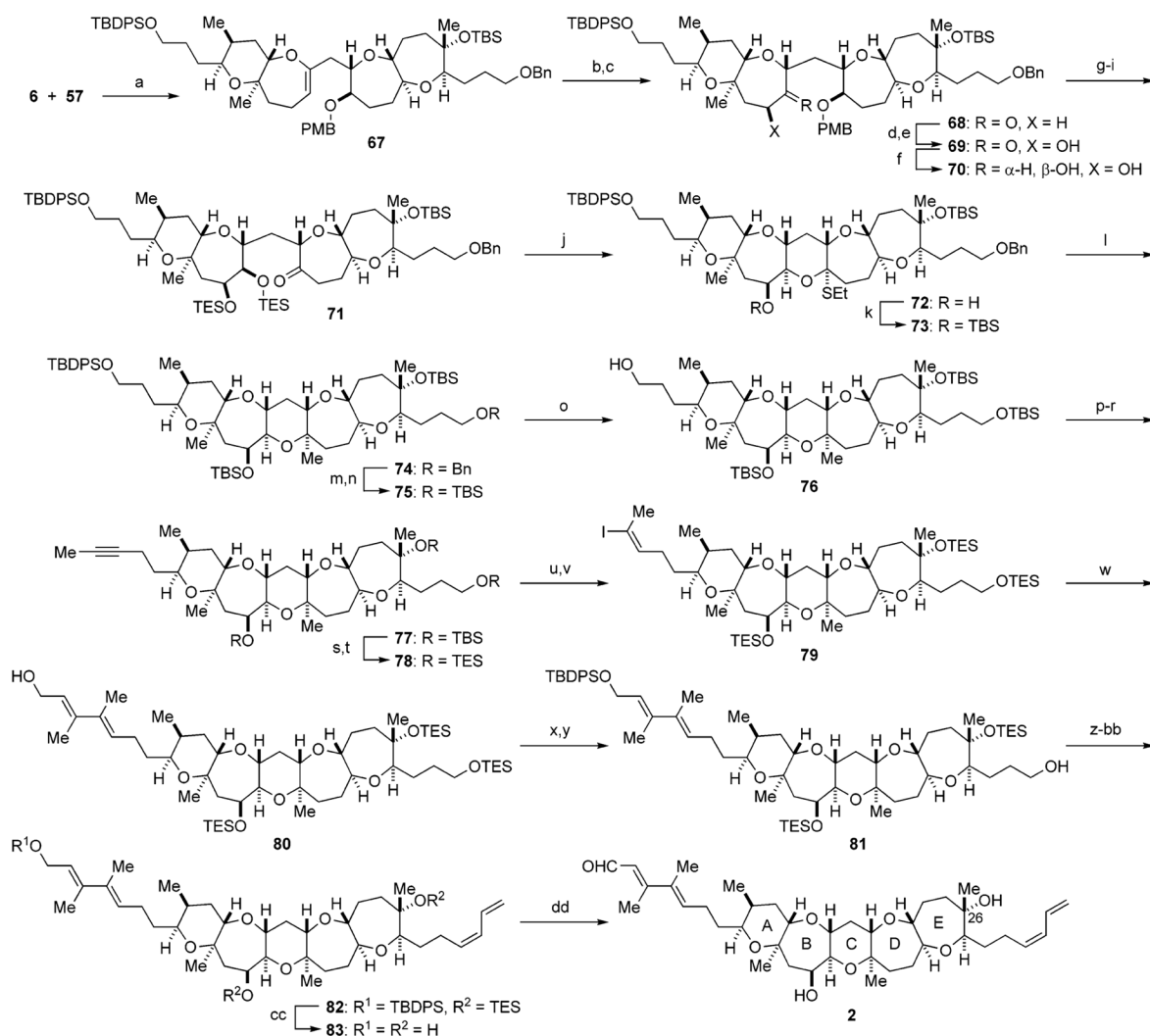


Figure 6.
Proposed biosynthetic pathway for marine polycyclic ether natural products.

**Scheme 8.****Synthesis of the 26-*epi*-DE Ring Fragment 57^a**

^a Reagents and conditions: (a) Cu(OAc)₂, PdCl₂, O₂, DMA/H₂O (7:1), rt, 92%; (b) TBAF, THF, rt; (c) methyl propiolate, NMM, CH₂Cl₂, rt, 96% (two steps); (d) SmI₂, MeOH, THF, rt, 57% for **60**, 37% for **61**; (e) LiAlH₄, THF, 0 °C, quant. from **60**, quant. from **61**; (f) TBSOTf, Et₃N, CH₂Cl₂, rt; (g) CSA, MeOH/CH₂Cl₂ (1:1), 0 °C, 90% (two steps); (h) SO₃•pyridine, Et₃N, DMSO/CH₂Cl₂ (1:1), 0 °C; (i) Ph₃P⁺CH₃Br⁻, NaHMDS, THF, 0 °C, 94% (two steps); (j) 9-BBN, THF, rt; then aq NaHCO₃, 30% H₂O₂, rt; (k) H₂, 20% Pd(OH)₂/C, MeOH, rt; (l) *p*-MeOC₆H₄CH(OMe)₂, PPTS, CH₂Cl₂, rt, 80% (three steps); (m) BnBr, KO^{*t*}-Bu, *n*-Bu₄NI, THF, rt; (n) DIBALH, CH₂Cl₂, -78 → 0 °C, 85% (two steps); (o) I₂, PPh₃, imidazole, benzene, rt; (p) KO^{*t*}-Bu, THF, 0 °C, 98% (two steps).



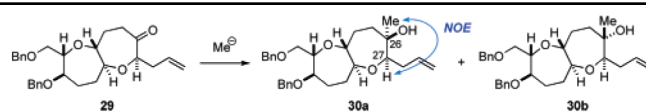
Scheme 9.

Total Synthesis of the Revised Structure 2 for Brevenal^a

^a Reagents and conditions: (a) **57**, 9-BBN, THF, rt; then 3 M aq Cs₂CO₃, **6**, Pd(PPh₃)₄, DMF, 50 °C; (b) BH₃•SMe₂, THF, rt; then aq NaHCO₃, 30% H₂O₂, rt, 81% (two steps); (c) TPAP, NMO, 4 Å molecular sieves, CH₂Cl₂, 0 °C, 98%; (d) LiHMDS, TMSCl, Et₃N, THF, -78 °C; (e) OsO₄, NMO, THF/H₂O (4:1), rt, 83% (two steps); (f) DIBALH, THF, -78 °C, 85% (+ diastereomer, 8%; recovered **69**, 3%); (g) TESOTf, Et₃N, CH₂Cl₂, 0 °C; (h) DDQ, CH₂Cl₂/pH 7 phosphate buffer (10:1), rt; (i) TPAP, NMO, 4 Å molecular sieves, CH₂Cl₂, rt, 88% (three steps); (j) EtSH, Zn(OTf)₂, CH₂Cl₂, rt, 51%; (k) TBSOTf, Et₃N, CH₂Cl₂, 0 °C → rt, 86%; (l) *m*CPBA, CH₂Cl₂, -78 °C; then Me₃Al (excess), -78 f 0 °C, 94%; (m) LiDBB, THF, -78 °C, 95%; (n) TBSOTf, Et₃N, CH₂Cl₂, 0 °C, 99%; (o) TBAF, AcOH, THF, rt, 79% after two recycles; (p) SO₃•pyridine, Et₃N, CH₂Cl₂/DMSO (3:1), 0 °C; (q) Bestmann reagent, K₂CO₃, MeOH, rt; (r) *n*-BuLi, THF/HMPA (10:1), -78 °C; then MeI, rt, 78% (three steps); (s) HF•pyridine, THF, rt, 97%; (t) TESOTf, Et₃N, CH₂Cl₂, 0 °C, 89%; (u) (Me₂PhSi)₂Cu(CN)Li₂, THF, -78 → 0 °C, regioselectivity = ca. 8.5:1; (v) NIS, MeCN/THF (3:1), rt, 88% (two steps), *E*:*Z* = ca. 6:1; (w) **5b**, Pd₂(dba)₃, Ph₃As, CuTC, DMSO/THF (1:1), rt, 60%; (x) TBDPSCl, imidazole, DMF, 0 °C, 87%; (y) PPTS, CH₂Cl₂/MeOH (4:1), 0 °C, 70%; (z) SO₃•pyridine, Et₃N, CH₂Cl₂/DMSO (4:1), 0 °C; (aa) **4**, *n*-BuLi, HMPA, THF, -78 °C → rt,

99% (two steps); (bb) 30% H₂O₂, NaHCO₃, THF, rt, 78%; (cc) TAS-F, THF/DMF (1:1), rt, quant.; (dd) MnO₂, CH₂Cl₂, rt, 76%.

Table 1

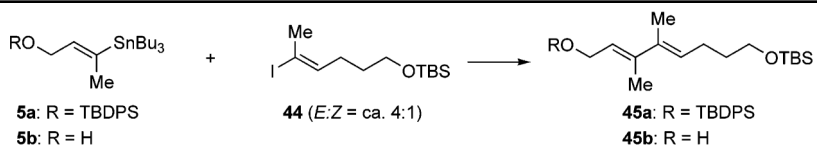
Stereoselective Methylation of Ketone **29**

entry	reagents and conditions	30a:30b	% yield ^a
1	Me ₃ Al (10 equiv), CH ₂ Cl ₂ , -78 °C → rt	1.3:1	78 (20) ^b
2	MeMgBr (10 equiv), THF, -78 °C	2.5:1	36 (52) ^b
3	MeMgBr (1.5 equiv), THF, -78 °C → rt	2.3:1	99
4	MeMgBr (1.5 equiv), toluene, -78 °C → rt	1:1.3	quant.
5	MeLi (1.2 equiv), THF, -78 °C → rt	10:1	97

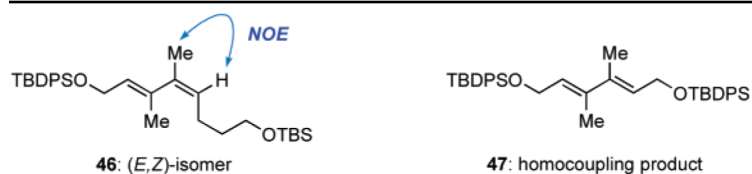
^a Isolated yields.

^b Yields in parentheses are recovered **29**.

Table 2
Stille Coupling of Vinyl Stannane **5** and Vinyl Iodide **44**



entry	vinyl stannane	reagents and conditions	% yield	(<i>E,E</i>):(<i>E,Z</i>)
1	5a	PdCl ₂ (MeCN) ₂ , DMF, rt → 45 °C	trace	nd ^a
2 ^b	5b	Pd ₂ (dba) ₃ , (2-furyl) ₃ P, CuI, DMSO/THF, rt	57	ca. 3.5:1
3 ^b	5b	Pd ₂ (dba) ₃ , Ph ₃ As, CuI, DMSO/THF, rt	54	ca. 5:1
4 ^b	5b	Pd ₂ (dba) ₃ , (2-furyl) ₃ P, CuI, DMSO/THF, 60 °C	48	1:1
5 ^b	5b	Pd ₂ (dba) ₃ , Ph ₃ As, CuI, DMSO/THF, 60 °C	66	1:1
6 ^b	5b	Pd ₂ (dba) ₃ , Ph ₃ As, CuTC, DMSO/THF, rt	84	ca. 10:1
7 ^c	5a	Pd ₂ (dba) ₃ , Ph ₃ As, CuI, DMSO/THF, rt	40	1:0
8 ^c	5a	Pd ₂ (dba) ₃ , Ph ₃ As, CuTC, DMSO/THF, rt	69	1:0



^a nd = not determined.

^b Isolated as a mixture of (*E,E*)- and (*E,Z*)-isomers. Ratio was estimated by ¹H NMR (600 MHz).

^c Isolated as an inseparable mixture of **45a** and homocoupling product **47**. Yield was estimated based on ¹H NMR analysis (600 MHz) of a purified mixture of **45a** and **47**.

Table 3
¹H NMR Chemical Shifts of Natural Product and Synthetic **1**^a

no.	natural brevenal ^b	synthetic 1	$\Delta\delta$	no.	natural brevenal ^b	synthetic 1	$\Delta\delta$
1	10.09	10.09	0.00	21	1.77	1.74	0.03
2	6.14	6.15	-0.01		2.16	2.13	0.03
3	—	—	—	22	3.35	3.22	0.12
4	—	—	—	23	3.17	3.22	-0.05
5	5.81	5.81	0.00	24	1.77	1.50	0.27
6	2.01	2.01	0.00		1.90	1.92	-0.02
	2.13	2.14	-0.01	25	1.52	1.52	0.00
7	1.09	1.08	0.01		1.54	1.69	-0.15
	1.47	1.49	-0.02	26	—	—	—
8	3.28	3.28	0.00	27	3.16	2.92	0.24
9	1.46	1.44	0.02	28	1.44	1.39	0.05
10	1.75	1.75	0.00		1.57	1.71	-0.14
	1.75	1.75	0.00	29	2.35	2.31	0.04
11	4.00	4.04	-0.04		2.35	2.31	0.04
12	—	—	—	30	5.45	5.39	0.06
13	2.23	2.23	0.00	31	6.10	6.10	-0.03
	2.32	2.35	-0.03	32	6.77	6.78	-0.01
14	4.08	4.10	-0.02	33	5.05	5.08	-0.03
15	3.45	3.47	-0.02		5.16	5.18	-0.02
16	3.71	3.75	-0.04	3-Me	1.80	1.78	0.02
17	1.85	1.86	-0.01	4-Me	1.55	1.55	0.00
	2.24	2.27	-0.03	9-Me	0.97	0.96	0.01
18	2.94	2.92	0.02	12-Me	1.18	1.19	-0.01
19	—	—	—	19-Me	1.13	1.14	-0.01
20	1.68	1.69	-0.01	26-Me	0.98	0.87	0.11
	1.77	1.69	0.08				

^a C₆HD₅ was adjusted to 7.15 ppm.

^b Chemical shift values were adjusted because in the original report (ref 8b) internal residual benzene was referenced to 7.16 ppm.

Table 4
 ^{13}C NMR Chemical Shifts of Natural Product and Synthetic **1**^a

no.	natural brevenal ^b	synthetic 1	$\Delta\delta$	no.	natural brevenal ^b	synthetic 1	$\Delta\delta$
1	191.0	190.7	0.3	21	29.8	29.6	0.2
2	126.0	126.0	0.0	22	86.3	85.6	0.7
3	156.7	156.1	0.6	23	84.8	83.9	0.9
4	135.8	135.8	0.0	24	29.4	29.4	0.0
5	134.6	134.6	0.0	25	38.8	37.4	1.4
6	26.4	26.4	0.0	26	73.9	74.3	-0.4
7	32.7	32.6	0.1	27	87.4	88.5	-1.1
8	70.9	70.7	0.2	28	30.6	29.9	0.7
9	33.4	33.4	0.0	29	25.3	24.8	0.5
10	35.3	35.2	0.1	30	133.0	132.9	0.1
11	76.5	76.4	0.1	31	130.1	130.2	-0.1
12	77.2	77.2	0.0	32	132.7	132.6	0.1
13	48.0	47.8	0.2	33	117.0	117.3	-0.3
14	69.9	69.9	0.0	3-Me	14.0	13.8	0.2
15	75.0	75.0	0.0	4-Me	13.7	13.7	0.0
16	73.7	73.6	0.1	9-Me	12.9	12.8	0.1
17	34.5	34.4	0.1	12-Me	19.5	19.3	0.2
18	82.0	82.1	-0.1	19-Me	16.2	15.8	0.4
19	76.7	76.7	0.0	26-Me	23.5	25.7	-2.2
20	37.8	37.5	0.3				

^a $^{13}\text{C}_6\text{D}_6$ was adjusted to 128.0 ppm.

^bChemical shift values were adjusted because in the original report (ref 8b) internal residual benzene was referenced to 128.4 ppm.