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Total Synthesis of Structurally Complex Marine Oxacyclic Natural Products

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Total synthesis of structurally complex marine oxacyclic natural products, (−)-gambierol, (−)-brevenal, and (+)-neopeltolide, has been accomplished by exploiting Suzuki–Miyaura coupling of enol phosphates, paving the way for biological investigations on these scarcely available substances.

Structurally complex, biologically active naturally occurring substances of marine origin continue to spur the interest of chemists and biologists.[1] The unusual and complex molecular architectures of marine natural products pose significant challenges to organic chemists and are a source of inspiration for the development of new organic reactions and innovative synthetic strategies. Meanwhile, marine natural products often exhibit potent biological activities with unique biochemical mode-of-action and serve as valuable molecular probes useful at the interface of chemistry and biology. However, in many cases, marine natural products are isolated in only minute quantities, and their constant supply from natural sources is problematic or virtually impossible. In addition, chemoselective derivatization of marine natural products themselves is usually quite difficult because of their sensitive and elaborate molecular structures, and access to their structural analogs is severely restricted in many cases. Since chemical synthesis is expected to be the only way to overcome these shortcomings, marine natural products are rewarding synthetic targets for organic chemists. In this Account, we describe the total synthesis of marine oxacyclic natural products (−)-gambierol, (−)-brevenal, and (+)-neopeltolide, which has been accomplished on the basis of Suzuki–Miyaura coupling of enol phosphates.

1. Convergent Strategy for the Synthesis of *trans*-Fused Polycyclic Ethers

1.1 Background. Marine polycyclic ether natural products are the secondary metabolites of marine unicellular algae, mainly dinoflagellates, and are structurally characterized by their unique *trans*-fused polycyclic ether skeletons (Figure 1).[2] Brevetoxin B, produced by the Florida red-tide dinoflagellate *Karenia brevis*, was the first member of this family of natural products to be structurally elucidated. In 1981, Nakanishi and co-workers reported the unprecedented ladder-shaped molecular structure of brevetoxin B on the basis of X-ray crystallographic analysis.[3] Since then, a number of polycyclic ether metabolites have been isolated and structurally characterized by state-of-the-art spectroscopic techniques. Despite the fact that marine polycyclic ether natural products share a common structural motif, they exhibit potent and diverse biological activities, including neurotoxicity, cytotoxicity, and antifungal activity. Among the members of this family of natural products, brevetoxins and ciguatoxins are known to specifically bind with high affinity to "site 5" of voltage-gated sodium channels (VGSCs) in excitable membranes and exert their potent neurotoxicity by altering the structures and functions of VGSCs.[4–6] However, the molecular basis of the agonistic activity of these neurotoxins on VGSCs is yet to be established. The most serious problem that hampers detailed biological investigations of marine polycyclic ether metabolites is, in many cases, their limited availability from natural sources. In addition, their extraordinary complex molecular structures are often resistant to selective chemical modifications, thereby precluding systematic structure–activity relationship studies.[7]

Under these circumstances, a number of synthetic organic chemists put their efforts toward the development of efficient strategies for the synthesis of *trans*-fused polycyclic ethers and their application to total synthesis.[8] The landmark achievements are the total synthesis of brevetoxins by the Nicolaou group[9,10] and the total synthesis of ciguatoxins by the Hirama group,[11,12] both of which have contributed to recent significant advances in the chemistry and biology of marine polycyclic ether natural products.[13]

1.2 A Convergent Strategy for the Synthesis of *trans*-Fused Polycyclic Ethers via Suzuki–Miyaura Coupling of Lactone-Derived Enol Triflates. Our own efforts in this area started with the development of a general, convergent strategy for the synthesis of *trans*-fused polycyclic ether skeletons, because it was apparent that the formation of cyclic ethers in a

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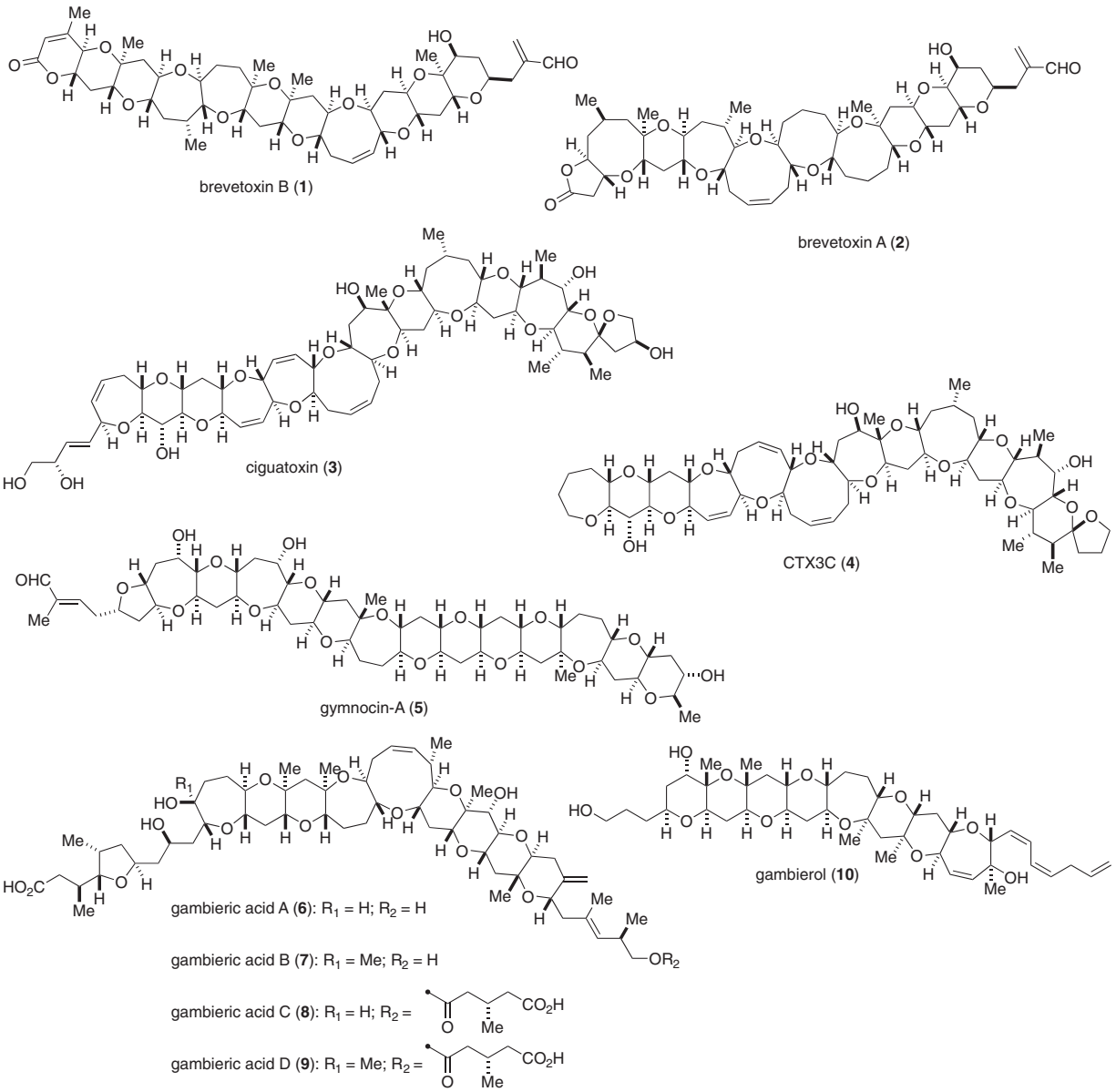


Figure 1. Structures of representative members of the family of marine polycyclic ether natural products.

one-by-one manner (i.e., linear strategy) was impractical for the construction of the huge molecular architecture of marine polycyclic ether natural products. We envisioned that stereoselective hydroboration of exocyclic enol ether **11** would generate the corresponding alkylborane **12** via axial hydride delivery, which without isolation would undergo Suzuki–Miyaura coupling[14,15] with lactone-derived enol triflate **13**[16] under the influence of a palladium catalyst and an aqueous base, affording endocyclic enol ether **14** (Figure 2). Stereoselective hydroboration of **14** and subsequent oxidation would deliver ketone **15**, which could be elaborated to mixed thioacetal **16** via deprotection and thioacetalization. Finally, reduction of the mixed thioacetal **16** would lead to *trans*-fused polycyclic ether **17**. In this manner, a diverse array of *trans*-fused polycyclic ethers could be efficiently built up from readily available cyclic ether fragments.[17]

To probe the viability of this idea, we first investigated Suzuki–Miyaura coupling of an alkylborane derived from

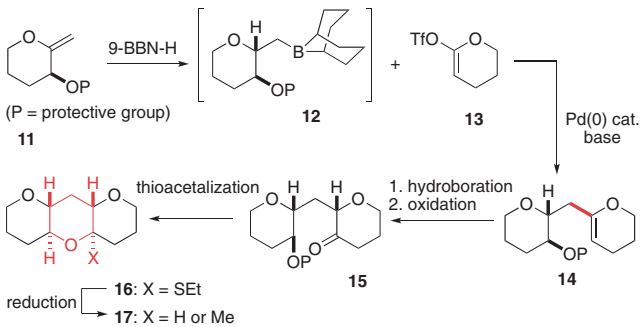
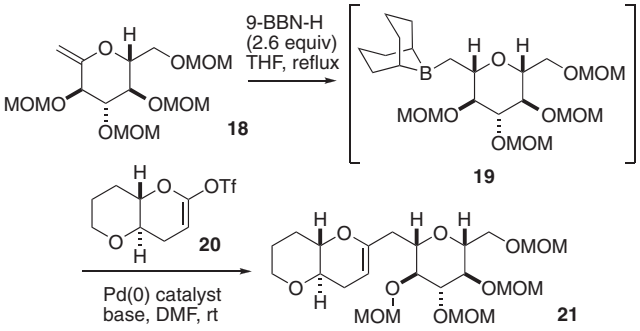


Figure 2. A convergent strategy for the synthesis of *trans*-fused polycyclic ethers via Suzuki–Miyaura couping of lactone-derived enol triflates.

exocyclic enol ether **18**[18] and lactone-derived enol triflate **20** as a model case (Table 1). In preliminary experiments, we found that hydroboration of **18** with 9-BBN-H proceeded with

Table 1. Suzuki–Miyaura Coupling of Lactone-Derived Enol Triflate **20** with Alkylborane **19**[a)]



Entry	Pd catalyst	Ligand	Base (equiv)	Yield/%
1	$[PdCl_2(dppf)]$	none	K_3PO_4 (1.5)	0
2	$[PdCl_2(dppf)]$	none	3 M aq K_3PO_4 (1.5)	40
3	$[PdCl_2(dppf)]$	none	3 M aq Cs_2CO_3 (1.5)	51
4	$[PdCl_2(dppf)]$	Ph_3As	3 M aq Cs_2CO_3 (1.5)	63
5	$[PdCl_2(dppf)]$	Ph_3As	3 M aq Cs_2CO_3 (3)	63
6	$[Pd_2(dba)_3]\cdot CHCl_3$	Ph_3As	3 M aq Cs_2CO_3 (3)	80

a) All coupling reactions were performed using $[PdCl_2(dppf)]$ (10 mol %) or $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol %), Ph_3As (40 mol %, for Entries 4–6), base, and KBr (1.2 equiv, for Entries 1–5) in DMF at room temperature. Enol triflate **20** was prepared from the corresponding lactone (1.5 equiv) and used immediately without purification.

complete stereocontrol to generate the corresponding alkylborane **19** and excess (2.6 equiv) 9-BBN-H was necessary for complete consumption of **18**. However, reaction of in situ generated alkylborane **19** with enol triflate **20** in the presence of $[PdCl_2(dppf)]$ (10 mol %) as a catalyst and K_3PO_4 (1.5 equiv) as a base in THF/DMF did not afford the desired endocyclic enol ether **21** at all (Entry 1). We surmised that the excess 9-BBN-H might reduce enol triflate **20** under palladium catalysis. Since it is well accepted that a small amount of water is normally tolerated in and sometimes even beneficial for Suzuki–Miyaura reactions, we examined the use of aqueous inorganic base to destroy the excess 9-BBN-H prior to the cross-coupling event. Thus, after completion of the hydroboration of **18**, aqueous K_3PO_4 (1.5 equiv) was added to the reaction mixture, and the resultant mixture was stirred at room temperature for 15 min.[19] This was then treated with enol triflate **20** and $[PdCl_2(dppf)]$ (10 mol %) in THF/DMF at room temperature. Gratifyingly, the desired endocyclic enol ether **21** was isolated in 40% yield under these conditions (Entry 2). Changing the base to aqueous Cs_2CO_3 was found to be beneficial (Entry 3). Further improvement was possible by running the reaction under Johnson's conditions,[20] where Ph_3As was used as a supporting ligand[21] (Entries 4 and 5). After several additional experiments, we found that the reaction was best carried out under the influence of $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol %) combined with Ph_3As (40 mol %) in the presence of aqueous Cs_2CO_3 (3 equiv) in THF/DMF at room temperature, and the yield of **21** could be improved up to 80% yield (Entry 6).

As summarized in Table 2, a variety of six-membered cyclic ether fragments could be cross-coupled in good to excellent yields under the optimized conditions, demonstrating the versatility of our strategy. More importantly, endocyclic enol ether **30** could be elaborated to pentacyclic ether **33** in only five steps (Figure 3). Thus, stereoselective hydroboration of **30** with thexylborane gave an alcohol, which was oxidized under Swern conditions to deliver ketone **31** in 82% yield as a single stereoisomer. Exposure of **31** to acidic methanol cleanly removed the acetonide and silyl protective groups to afford hemiacetal **32** after acetylation. Finally, treatment of **32** with Et_3SiH and $BF_3\cdot OEt_2$[22] furnished pentacyclic ether **33** in 83% yield as a single stereoisomer. This result clearly demonstrates that we are now able to build up complex *trans*-fused polytetrahydropyran ring systems in a rapid and efficient manner.[23]

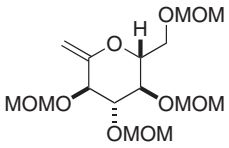
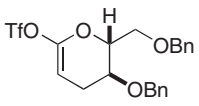
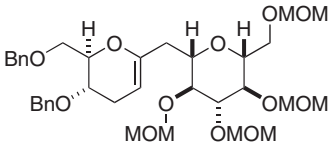
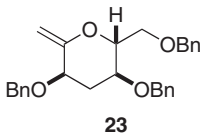
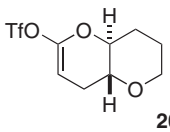
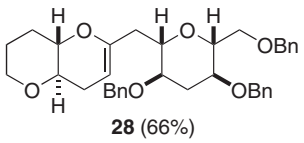
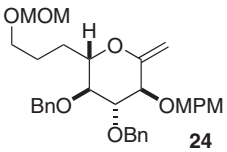
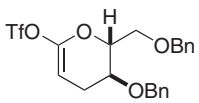
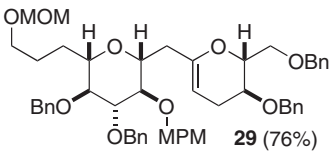
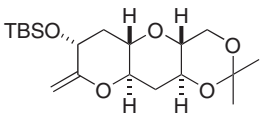
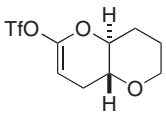
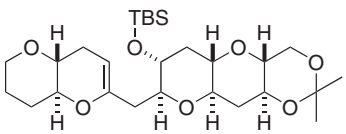
1.3 Enol Phosphates: A Surrogate for Triflates. Having established a reliable strategy for the assembly of *trans*-fused polytetrahydropyrans, our attention next turned to the synthesis of *trans*-fused polycyclic ethers containing medium-sized cyclic ethers. Thus, we first attempted to couple an alkylborane generated from exocyclic enol ether **34** and seven-membered lactone-derived enol triflate **35** under the optimized conditions (Figure 4). However, we could not detect even a trace amount of the desired endocyclic enol ether **36**. Changing the base to aqueous $NaHCO_3$ did afford **36** but in only 27% yield. These results could be ascribed to the instability of enol triflate **35** under the alkaline reaction conditions, resulting in rapid decomposition. This unfruitful experience led us to consider the use of lactone-derived enol phosphates as an electrophilic component in Suzuki–Miyaura coupling.

Ever since Oshima and co-workers first reported a palladium-catalyzed coupling of enol phosphates with organoaluminum reagents in 1980,[24] the synthetic community had paid little attention to the potential utility of enol phosphates in palladium-catalyzed cross-coupling reactions.[25] A breakthrough came from the Nicolaou group in 1997, which showed that lactone-derived enol phosphates are more stable and easier-to-handle than the corresponding triflates and display sufficient reactivity toward Stille, Sonogashira, Negishi, and alkoxycarbonylation reactions.[26] Prompted by their findings, we decided to investigate the use of lactone-derived enol phosphates in Suzuki–Miyaura coupling.

To probe the reactivity of lactone-derived enol phosphates, we examined Suzuki–Miyaura coupling of an alkylborane generated from exocyclic enol ether **34** and enol phosphate **38** as model substrates (Table 3). It was immediately found that palladium complexes with "soft" ligands such as Ph_3As or $(2\text{-furyl})_3P$[21] were completely ineffective for the present case, presumably due to the low reactivity of enol phosphates toward oxidative addition to the palladium(0) species (Entries 1 and 2). Therefore, we changed the catalyst to $[Pd(PPh_3)_4]$, a classical palladium complex with electron-rich supporting ligands. This idea proved to be rewarding; when the reaction was performed under the influence of $[Pd(PPh_3)_4]$ as the catalyst and aqueous K_3PO_4 as the base (DMF, 50 °C), the desired cross-coupled product **39** was isolated in moderate yield (Entry 3). Improvement of the product yield was possible by switching the base to aqueous $NaHCO_3$ and by increasing the amount of enol phosphate **38** (Entries 4–7).

To investigate the versatility of the reaction, an array of medium-sized lactone-derived enol phosphates were prepared and tested (Table 4). We were delighted to find that all of the

Table 2. Application to a Variety of Six-Membered Lactone-Derived Enol Triflates[a)]

Exocyclic enol ether	Enol triflate	Coupling product
 **22**	 **26**	 **27** (61%)
 **23**	 **20**	 **28** (66%)
 **24**	 **26**	 **29** (76%)
 **25**	 **20**	 **30** (66%)

a) All coupling reactions were performed using [$PdCl_2$(dppf)] (10 mol %), Ph_3As (40 mol %), aqueous Cs_2CO_3 (3 equiv), and KBr (1.2 equiv) in DMF at room temperature. Enol triflates were prepared from the respective lactones (1.5 equiv) and used immediately without purification.

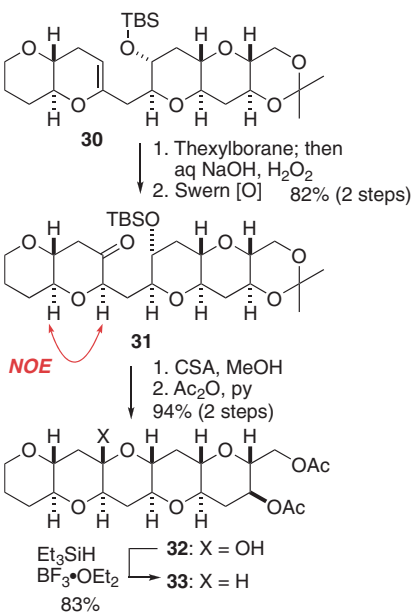


Figure 3. Convergent synthesis of pentacyclic ether **33**.

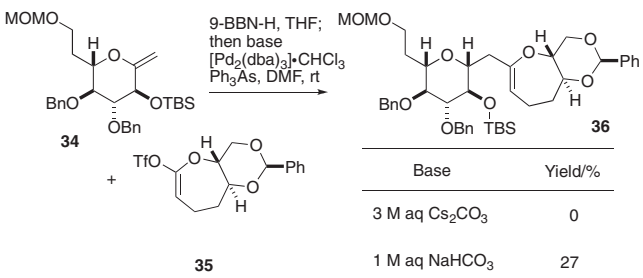


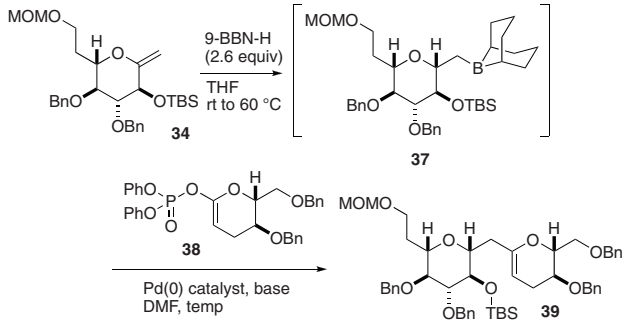
Figure 4. Suzuki–Miyaura coupling of seven-membered lactone-derived enol triflate **35**.

lactone-derived enol phosphates **40**–**44**, ranging in size from six- to nine-membered, successfully cross-coupled with in situ generated alkylborane **37**, affording the respective cross-coupled product (i.e., **36** and **45**–**48**) in excellent yields. These results demonstrated the versatility of our strategy for the synthesis of a diverse set of *trans*-fused polycyclic ethers containing medium-sized ring ethers.[27]

2. Total Synthesis of (−)-Gambierol

2.1 Background. In 1993, Satake et al. reported the isolation of gambierol (**10**, Figure 1) from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*.[28] Its gross structure including relative stereochemistry has been characterized on the basis of extensive 2D NMR studies and the absolute configuration was later determined by chemical derivatization and application of the modified Mosher's analy-

Table 3. Suzuki–Miyaura Coupling of Lactone-Derived Enol Phosphate **38** with Alkylborane **37**[a)]



Entry	Pd catalyst	Ligand	Base	**38** /equiv	Temp /°C	Yield /%
1	$[Pd_2(dba)_3]$ $\cdot CHCl_3$	Ph_3As	aq Cs_2CO_3	1.0	rt	0
2	$[Pd_2(dba)_3]$ $\cdot CHCl_3$	$(2\text{-furyl})_3P$	aq Cs_2CO_3	1.0	rt	0
3	$[Pd(PPh_3)_4]$	none	aq K_3PO_4	1.0	rt	46
4	$[Pd(PPh_3)_4]$	none	aq K_3PO_4	1.0	50	56
5	$[Pd(PPh_3)_4]$	none	aq $NaHCO_3$	1.0	50	72
6	$[Pd(PPh_3)_4]$	none	aq $NaHCO_3$	1.4	50	84
7	$[Pd(PPh_3)_4]$	none	aq $NaHCO_3$	2.0	50	98

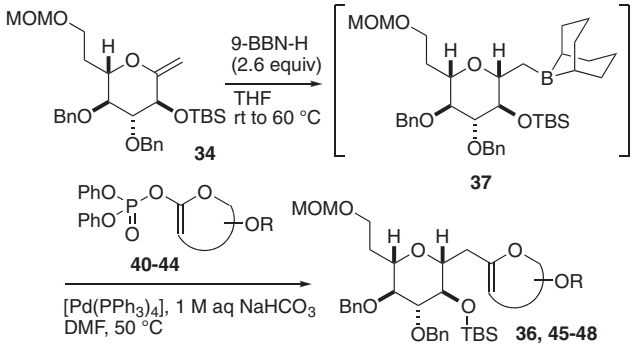
a) All coupling reactions were performed using $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol %) or $[Pd(PPh_3)_4]$ (10 mol %), Ph_3As or $(2\text{-furyl})_3P$ (40 mol %, for Entries 1 and 2), base (3 equiv), and enol phosphate **38** (1.0–2.0 equiv) in DMF at indicated temperature.

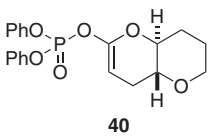
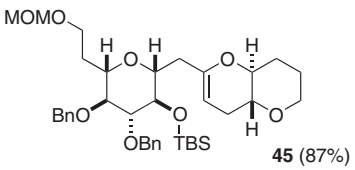
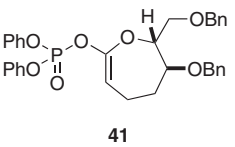
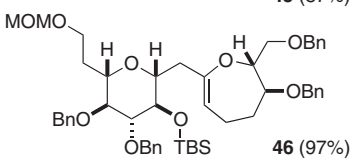
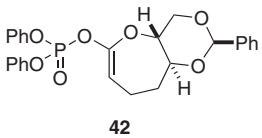
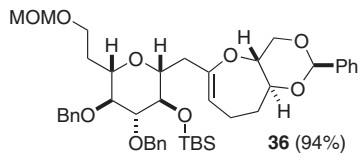
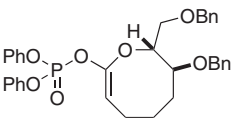
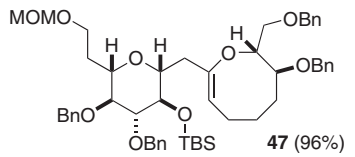
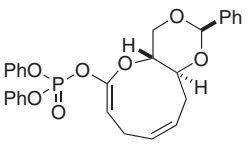
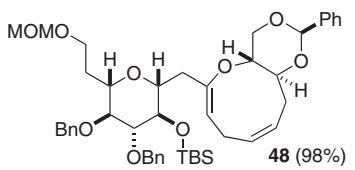
sis.[29] The molecular structure of **10** is comprised of the octacyclic polyether skeleton attached with a partially skipped triene side chain. The biological activity of gambierol is quite intriguing in that it displays potent neurotoxicity against mice with a LD_{99} value of 50 μg kg^{-1} (ip) with neurological symptoms that resemble to those caused by ciguatoxins. This implies a possible role of gambierol in ciguatera fish poisoning, one of the most widespread seafood poisonings of non-bacterial origin. However, the limited availability of gambierol from natural sources precluded further detailed biological investigations.

In 2002, we reported the total synthesis of (−)-gambierol, the naturally occurring enantiomer, for the first time.[30,31] The total synthesis of (−)-**10** was founded on our developed convergent strategy for the synthesis of *trans*-fused polycyclic ethers. Soon thereafter, the Kadota/Yamamoto group independently reported the second total synthesis of (−)-**10** based on their intramolecular allylation/ring-closing metathesis strategy.[32] Since then, three additional total and formal syntheses of (−)-**10** have been recorded.[33–36]

2.2 Synthesis Plan. Our total synthesis of (−)-**10** centered on the Suzuki–Miyaura coupling-based convergent strategy, as illustrated in Figure 5. Since the sensitive triene side chain must be introduced at a late stage of the total synthesis, we planned Stille coupling of (*Z*)-vinyl bromide **49** with (*Z*)-vinylstannane **50** for the construction of the triene side chain. We envisioned that the octacyclic polyether core **51** could be divided into the ABC-ring exocyclic enol ether **52** and the EFGH-ring enol phosphate **53**.

Table 4. Application to a Variety of Medium-Sized Lactone-Derived Enol Phosphates[a)]



Enol phosphate	Coupling product
 **40**	 **45** (87%)
 **41**	 **46** (97%)
 **42**	 **36** (94%)
 **43**	 **47** (96%)
 **44**	 **48** (98%)

a) All coupling reactions were performed using $[Pd(PPh_3)_4]$ (10 mol %), 1 M aqueous $NaHCO_3$ (3 equiv), and enol phosphate (2 equiv) in DMF at 50 °C.

2.3 Synthesis of the ABC-Ring Fragment. The synthesis of the ABC-ring fragment **52** started with the known silyl ether **54**,[37] corresponding to the B-ring (Figure 6). Oxidative cleavage of the double bond within **54**, Horner–Wadsworth–Emmons reaction of the derived aldehyde, and subsequent DIBALH reduction gave allylic alcohol **55**. Sharpless asymmetric epoxidation of **55** yielded an epoxy alcohol, which was regioselectively reduced with Red-Al® to deliver 1,3-diol **56**.[38] Protection of **56** as its anisylidene acetal followed by its regioselective reductive cleavage with DIBALH gave alcohol **57**. Oxidation, homologation with a stabilized ylide, and

removal of the silyl group afforded hydroxy enoate **58**. The A-ring was forged stereoselectively by exposure of hydroxy enoate **58** to NaH in THF at room temperature, which led to ester **59** in 86% yield as a single stereoisomer. DIBALH reduction of **59** to the corresponding aldehyde was followed by Wittig methylenation to give olefin **60**. At this stage, the newly generated C4 and C6 stereogenic centers were confirmed by NOE experiments. Olefin **60** was hydroborated with 9-BBN-H to give the corresponding primary alcohol, which was then elaborated to alcohol **61** via standard protective group chemistry. After TPAP/NMO oxidation[39] of **61**, Tebbe methylenation[40] of the derived aldehyde gave olefin **62**, which was converted to allylic alcohol **63** via a four-step sequence that involves hydroboration, oxidation, Horner–Wadsworth–Emmons reaction, and DIBALH reduction. Treatment of allylic alcohol **63** with *m*-CPBA afforded epoxy alcohol **64** as a single diastereomer. Oxidation, Wittig methylenation, and desilylation led to vinyl epoxide **65**, which, on treatment with PPTS, underwent 6-*endo* cyclization[41] to furnish the tricyclic ether **66**. The newly generated C13 and C14 stereogenic centers were confirmed by an NOE experiment and a large $^{3}J_{\text{H-13,H-14}}$ value. Protection of the resultant alcohol, oxidative cleavage of the vinyl group, and subsequent $NaBH_4$ reduction gave alcohol **67**, which was iodinated and then treated with KO*t*-Bu to furnish the ABC-ring fragment **52**.

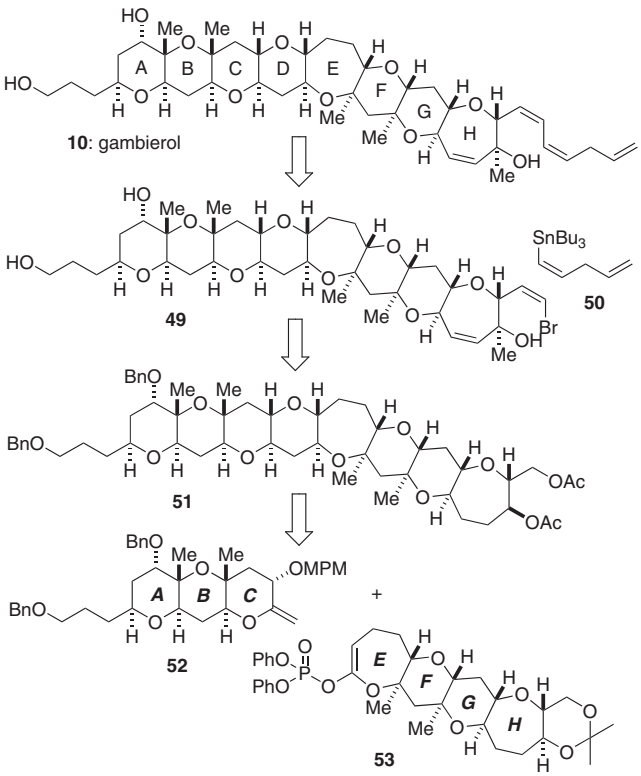


Figure 5. Synthesis plan toward gambierol.

2.4 Synthesis of the EFGH-Ring Fragment. The synthesis of the EFGH-ring fragment **53** commenced with the known enoate **68**[10c] (Figure 7). Ozonolysis of **68** followed by reductive workup with $NaBH_4$ gave alcohol **69**. Iodination of **69** followed by reaction with 2-lithio-1,3-dithiane yielded, after desilylation, alcohol **70**. Treatment of **70** with ethyl propiolate/NMM and ensuing hydrolysis of the 1,3-dithiane delivered aldehyde **71**, which was exposed to SmI_2 in THF/MeOH at room temperature, a procedure reported by Nakata and coworkers.[42] This afforded the tricyclic lactone **72** that corresponds to the H-ring. DIBALH reduction followed by Wittig

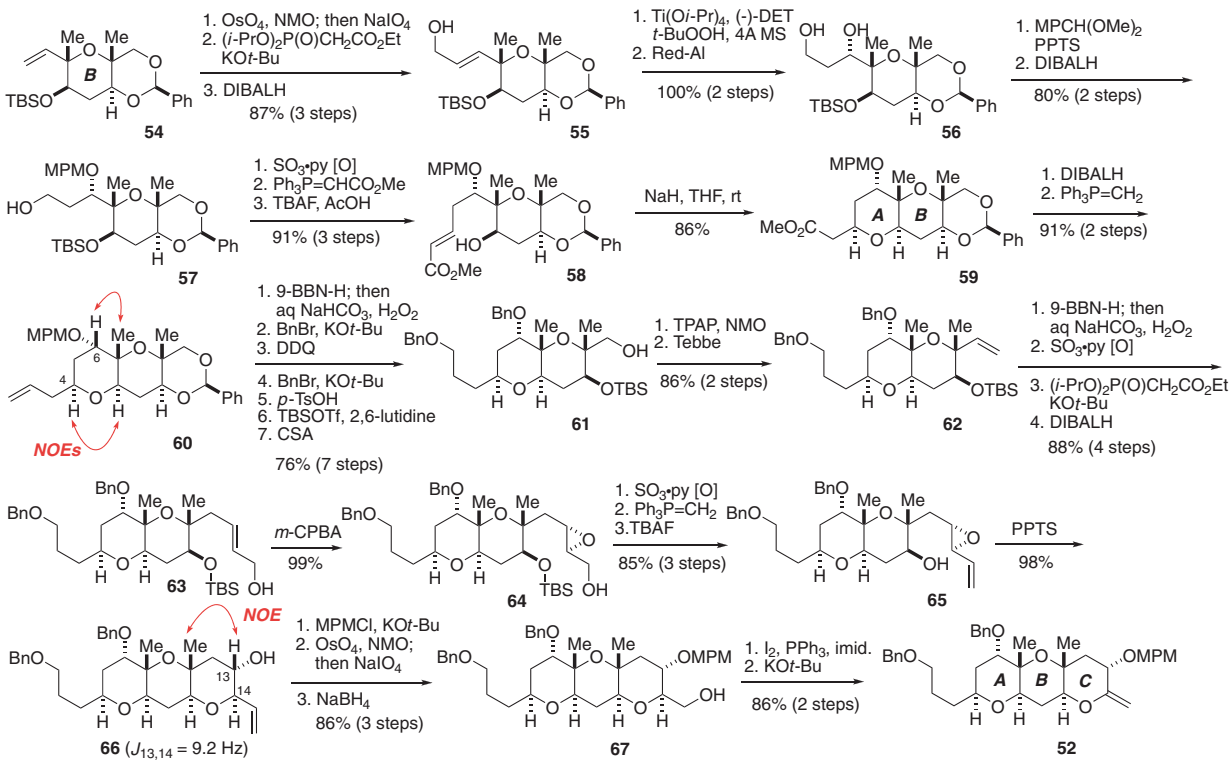


Figure 6. Synthesis of the ABC-ring fragment **52** of gambierol.

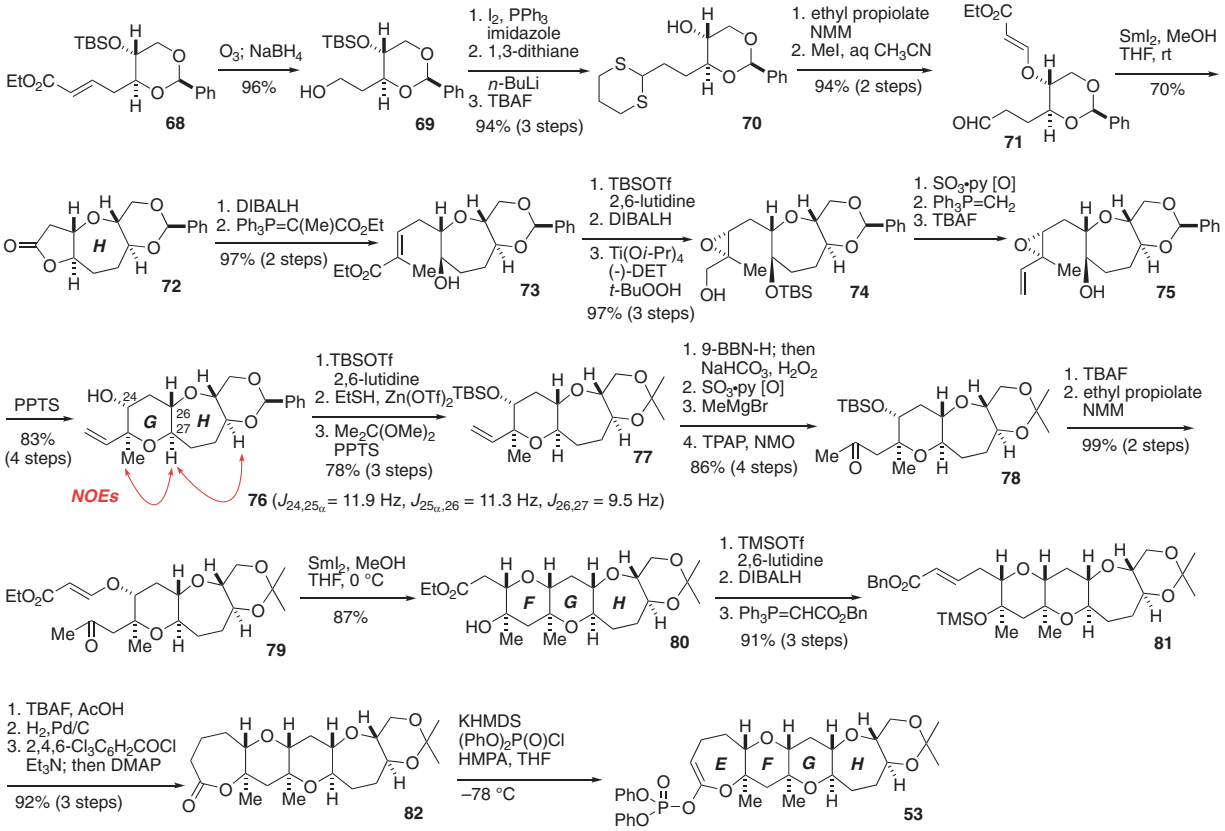


Figure 7. Synthesis of the EFGH-ring fragment **53** of gambierol.

reaction gave alcohol **73**. After silylation and reduction, Sharpless asymmetric epoxidation of the derived allylic alcohol delivered epoxy alcohol **74** as a single stereoisomer. Oxidation, Wittig methylenation, and desilylation led to vinyl epoxide **75**, which participated in 6-*endo* cyclization under acidic conditions to furnish the tricyclic ether **76**. The relative stereochemistry of **76** was established by NOE experiments and $^{3}J_{H,H}$ value analysis. After a three-step protective group manipulation, the resultant olefin **77** was hydroborated with 9-BBN-H to give an alcohol, which was converted to methyl ketone **78** via oxidation, methylation, and oxidation. Deprotection of the silyl group of **78** followed by reaction of the resultant alcohol with ethyl propiolate/NMM yielded β-alkoxy acrylate **79**. Treatment of **79** with SmI_2 in THF/MeOH at 0 °C effected stereoselective reductive cyclization to afford tetracyclic ether **80** as a single stereoisomer. After silylation, half-reduction of the derived ester to the corresponding aldehyde and subsequent reaction with a stabilized ylide gave enoate **81**. Deprotection of the silyl group, hydrogenation, and Yamaguchi lactonization[43] of the derived hydroxy acid afforded lactone **82**. Finally, enolization of **82** with KHMDS in the presence of $(PhO)_2P(O)Cl$ furnished the EFGH-ring fragment **53**.

2.5 Assembly of Two Advanced Fragments and Completion of the Total Synthesis. With the two key intermediates in hand, we proceeded to construct the octacyclic polyether core **51** as depicted in Figure 8. Stereoselective hydroboration of exocyclic enol ether **52** with 9-BBN-H produced an alkylborane, which was in situ coupled with enol phosphate **53** in the presence of aqueous Cs_2CO_3 and $[PdCl_2(dppf)]\cdot CH_2Cl_2$ catalyst to afford endocyclic enol ether **83** in 86% yield. Hydroboration of **83** with $BH_3\cdot$THF proceeded in a stereoselective manner to give, after oxidative workup, an alcohol, which was oxidized with TPAP/NMO to deliver ketone **84** as a single stereoisomer. Deprotection of the MPM group, mixed thioacetalization[30a,30b] with concomitant removal of the acetonide (EtSH and $Zn(OTf)_2$), and acetylation of the resultant diol then led to mixed thioacetal **85** in 75% yield for the three steps. Finally, stereoselective desulfurization of **85** (Ph_3SnH, AIBN, toluene, 110 °C)[44] furnished octacyclic ether **51**. Thus, the octacyclic polyether skeleton **51** was efficiently constructed from the two advanced intermediates **52** and **53** in only seven steps, demonstrating the efficiency and applicability of our convergent strategy.

Completion of the total synthesis of (−)-**10** is summarized in Figure 9. Removal of the acetate groups from **51**, selective silylation of the liberated primary alcohol, and ensuing oxidation of the remaining secondary alcohol gave ketone **86**. The H-ring double bond was incorporated via the Ito–Saegusa procedure.[45] Thus, enolization of **86** with LHMDS in the presence of $TMSCl/Et_3N$ gave the corresponding enol silane, which was oxidized with $Pd(OAc)_2$ to deliver an enone. This was reacted with MeMgBr (toluene, −78 °C)[46] to afford tertiary alcohol **87** as a single stereoisomer. Standard protective group chemistry allowed elaboration of **87** to alcohol **88** in a five-step sequence. The requisite (*Z*)-vinyl bromide unit for the construction of the triene side chain was installed via oxidation, Corey–Fuchs dibromoolefination,[47] and stereoselective reduction of the derived dibromoolefin,[48] leading to (*Z*)-vinyl

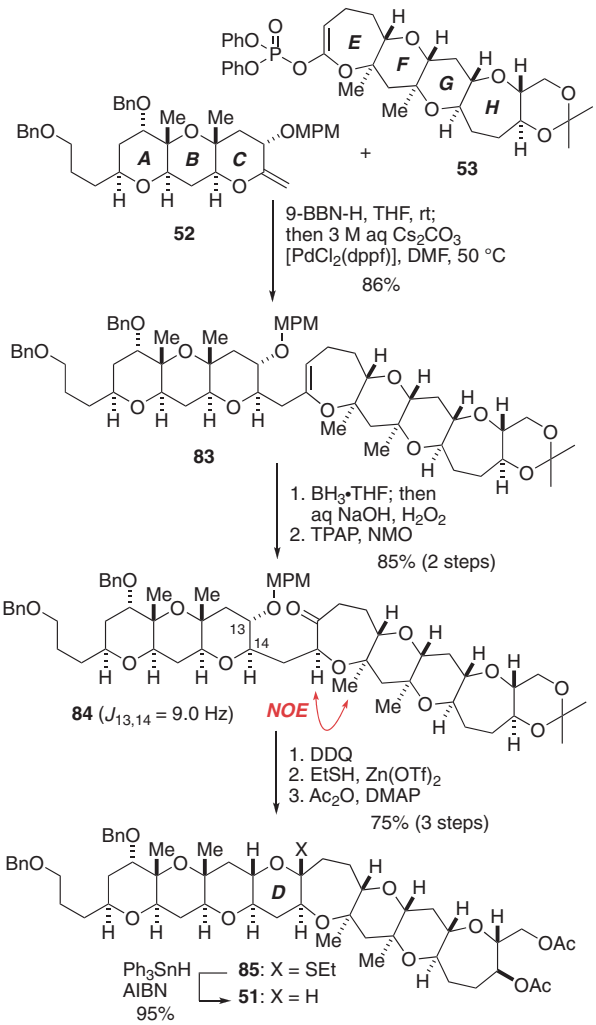


Figure 8. Convergent synthesis of the octacyclic polyether core of gambierol.

bromide **89**. Stille coupling of **89** with (*Z*)-vinyl stannane **50**[49] was best accomplished under the copper(I)-accelerated modified conditions developed by Corey et al. ([$Pd(PPh_3)_4$], CuCl, LiCl, DMSO/THF, 60 °C),[50] which afforded protected gambierol **90**. Unfortunately, all attempts at removing the three silyl groups of **90** turned out to be unrewarding; the sensitive triene side chain underwent degradation upon treatment of **90** with TBAF, HF•pyridine, 3HF•Et_3N, while the sterically encumbered C30 TBS group resisted buffered HF•pyridine or TASF.[51] At this stage, we thought that it would be possible to remove the silyl groups *before* the introduction of the sensitive triene. Accordingly, we found that exposure of **89** to excess HF•pyridine afforded triol **49** in quantitative yield. Finally, Stille coupling of **49** with **50** under the modified conditions furnished (−)-gambierol (i.e., (−)-**10**) in 43% yield. The spectroscopic properties of the synthetic material including ^{1}H, ^{13}C NMR, HRMS, and CD spectra were in full accordance with those of an authentic sample, thereby confirming the complete stereostructure of this natural product. Furthermore, the acute toxicity of the synthetic material against mice was comparable to that of the naturally occurring compound. Thus, the total synthesis of (−)-gambierol was accomplished for the first time, which proceeded in 71 steps (longest linear sequence). Considering the size and complexity of the target molecule, the present total synthesis is highly convergent and flexible. Significantly, the total synthesis allowed to us to produce synthetic gambierol in quantities up to 200 mg for detailed biological investigations.[52,53] Also, we were able to synthesize a wide variety of structural analogs toward systematic elucidation of the structure–activity relationships of this natural product.[54]

3. Total Synthesis of (−)-Brevenal

3.1 Background. In 2004, Bourdelais and co-workers reported the isolation and structure characterization of (−)-brevenal, a new member of the family of polycyclic ether natural products.[55] This naturally occurring substance is a secondary metabolite of the Florida red-tide causative dinoflagellate *K. brevis*. The gross structure including the relative stereochemistry of brevenal was characterized on the basis of extensive 2D NMR analysis as represented by structure **91**, but the absolute configuration remained undetermined (Figure 10). Although the size of the molecule is relatively compact when compared to other marine polycyclic ether metabolites, the pentacyclic polyether core densely arranged with four methyl groups, two hydroxy groups, and a heavily substituted left-hand (*E*,*E*)-dienal side chain poses a significant synthetic challenge. Importantly, brevenal competitively displaces tritiated dihydrobrevetoxin B ([^{3}H]-PbTx-3) from VGSCs derived from rat brain synaptosomes in a dose dependent manner and antagonizes in vivo effects of brevetoxins, thus representing a natural brevetoxin antagonist. It has recently been shown that brevenal is a potent inhibitor of ciguatoxin-induced neurotoxicity.[56] Furthermore, Abraham et al. reported that in an animal model of asthma, brevenal improves tracheal mucus velocity in picomolar concentrations to the same degree as that observed with micromolar concentrations of a sodium channel blocker, amiloride, which is in clinical use for treatment of cystic fibrosis.[57] These biological aspects of brevenal make it an attractive potential lead compound for the development of novel therapeutic agents for treatment of mucociliary dysfunction associated with cystic fibrosis and other lung diseases.

Intrigued by the synthetically challenging structure and unique biological activities, we launched a program toward the total synthesis of (−)-brevenal by exploiting our convergent strategy based on Suzuki–Miyaura coupling. Consequently, it was found that the ^{1}H and ^{13}C NMR spectroscopic data of synthetic **91** did not match those reported by Bourdelais et al.[55] Careful inspection of the ^{1}H and ^{13}C NMR spectra and NOE correlations of synthetic **91** and natural product suggested that the relative stereochemistry of the C26 quaternary center would have been incorrectly assigned. This assumption was also supported by the biosynthetic hypothesis for marine polycyclic ether metabolites independently proposed by Nakanishi and Shimizu[58] (vide infra). Accordingly, we proposed the revised structure of (−)-brevenal as represented by structure **92**, which was finally validated by our total synthesis. The absolute configuration was determined at the same time by comparing the specific rotation of synthetic **92** with that of a natural sample. Thus, we unequivocally established the complete stereostructure of (−)-brevenal to be the structure represented by **92** through our total synthesis.[59] Recently, the second total

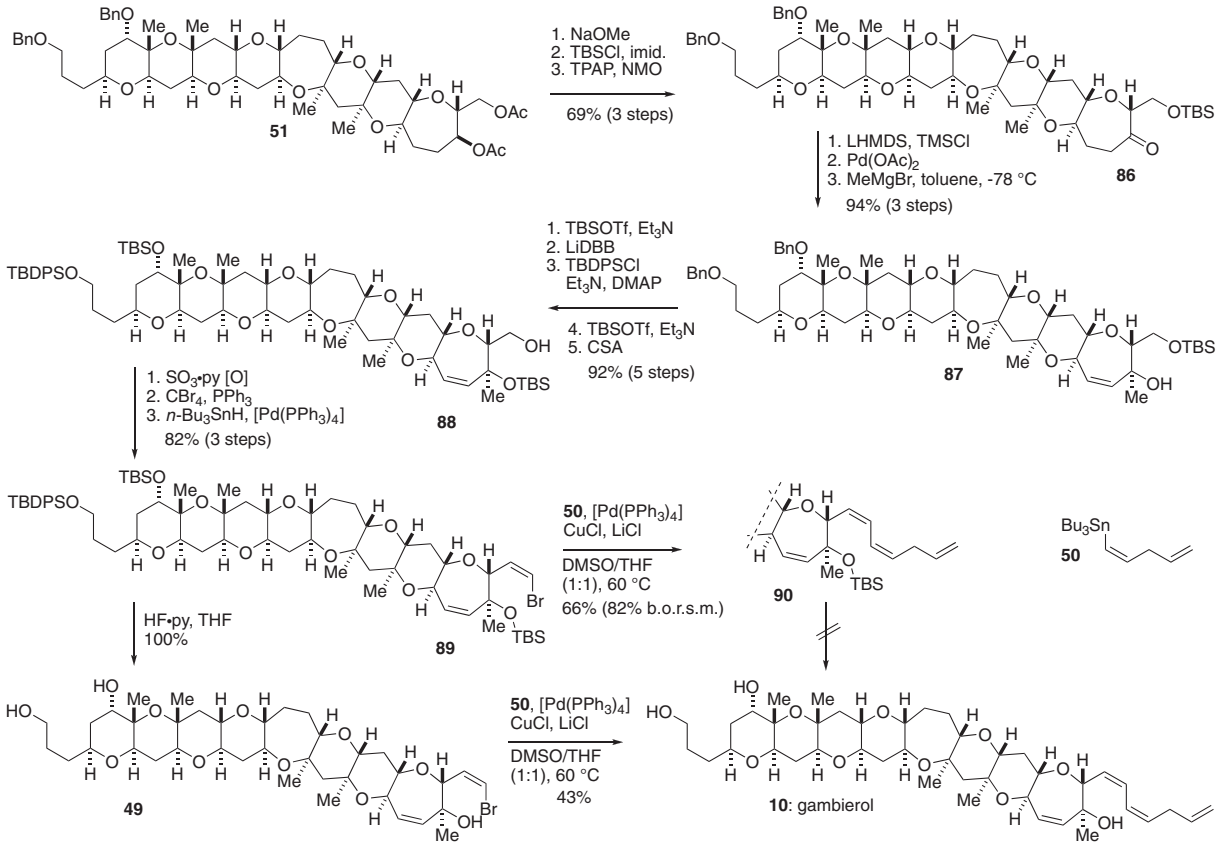


Figure 9. Completion of the total synthesis of gambierol.

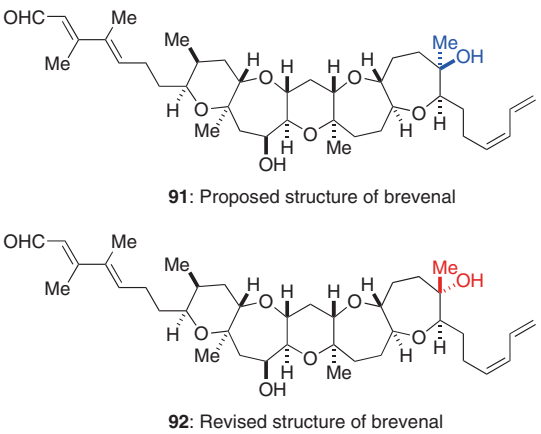


Figure 10. The proposed structure **91** and the revised structure **92** of (−)-brevenal.

synthesis of this natural product has been described by Kadota and co-workers.[60] In the following sections, we describe the details of these structural and synthetic endeavors on (−)-brevenal.

3.2 Synthesis Plan. We planned the total synthesis of the originally proposed structure **91** as delineated in Figure 11. The apparently sensitive unsaturated side chains positioned at each end of the molecule were to be sequentially incorporated at a late stage of the total synthesis. The pentacyclic polyether core **93** could be divided into the AB-ring enol phosphate **94** and the DE-ring exocyclic enol ether **95** by exploiting our convergent strategy based on Suzuki–Miyaura coupling.

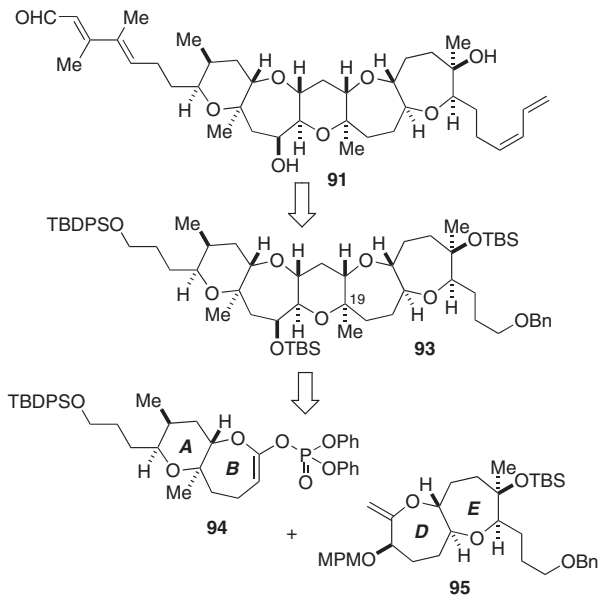


Figure 11. Synthesis plan toward the proposed structure **91** of brevenal.

3.3 Synthesis of the AB-Ring Enol Phosphate. The synthesis of the AB-ring enol phosphate **94** started with Evans asymmetric aldol reaction[61] of aldehyde **96** with oxazolidinone **97**, which was followed by reductive removal of the chiral auxiliary[62] to deliver 1,3-diol **98** as a single diastereomer (Figure 12). This was converted to allylic alcohol **99** by a

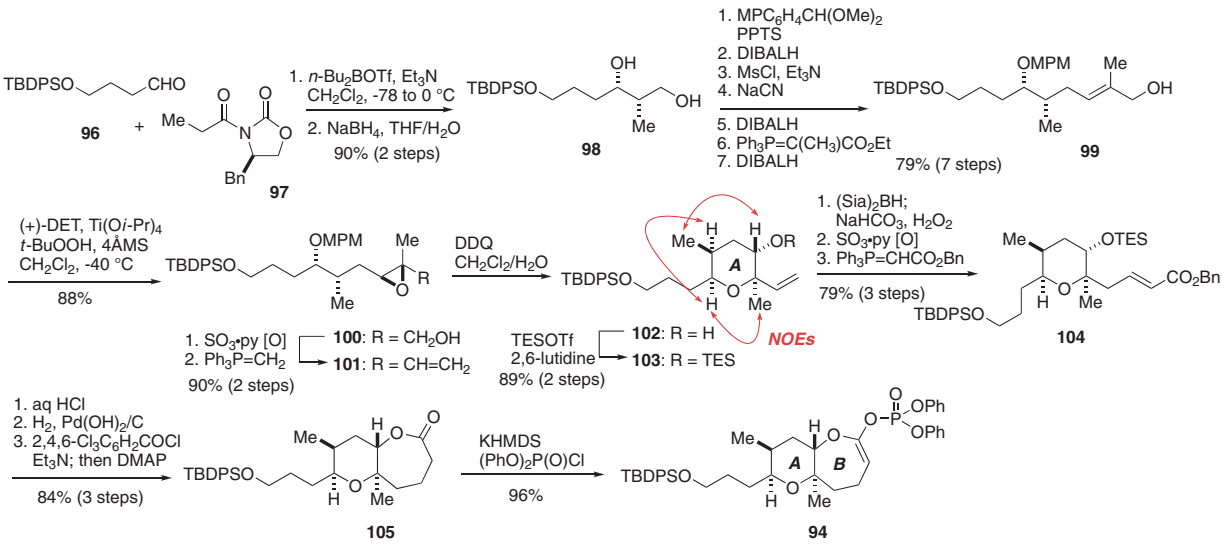


Figure 12. Synthesis of the AB-ring fragment **94** of brevenal.

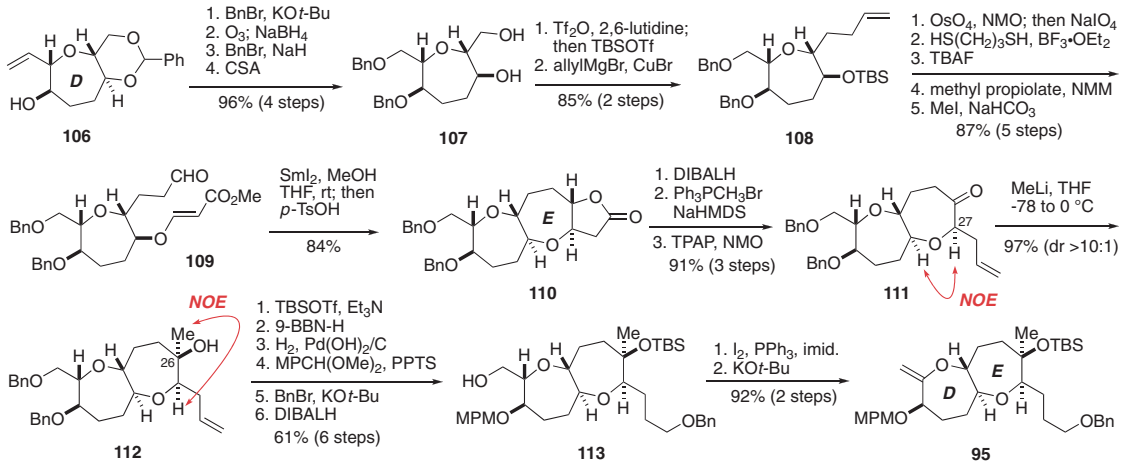


Figure 13. Synthesis of the DE-ring fragment **95** of the proposed structure **91** of brevenal.

standard, seven-step sequence. Sharpless asymmetric epoxidation of **99** led to epoxy alcohol **100**, which was oxidized and then methylenated to give vinyl epoxide **101**. Upon treatment of **101** with DDQ, removal of the MPM group and subsequent 6-*endo* cyclization took place smoothly in a domino fashion[63] to afford alcohol **102** that corresponds to the A-ring of (−)-brevenal. The relative stereochemistry of **102** was established by NOE experiments as shown. After silylation, the resultant silyl ether **103** was transformed to enolate **104** via hydroboration, oxidation, and Wittig reaction. Following removal of the TES group under mild acidic conditions, hydrogenation/hydrogenolysis gave a hydroxy acid, which was lactonized to afford seven-membered lactone **105**. This was treated with KHMDS/$(PhO)_2P(O)Cl$ to furnish the AB-ring enol phosphate **94**.

3.4 Synthesis of the DE-Ring Exocyclic Enol Ether. The synthesis of the DE-ring exocyclic enol ether **95** commenced with the known alcohol **106**[36c] that corresponds to the D-ring (Figure 13). A four-step sequence involving benzylation, ozonolysis/reduction, benzylation, and deprotection of the benzylidene acetal gave diol **107**. Application of one-pot selective triflation/silylation[64] followed by alkylation of the resultant triflate with allylmagnesium bromide/CuBr[65] yielded olefin **108**, which was converted to aldehyde **109** in five steps. Exposure of **109** to SmI_2 in THF/MeOH at room temperature delivered, after acid treatment, lactone **110** as a single stereoisomer. DIBALH reduction of **110** followed by Wittig methylenation, and subsequent TPAP/NMO oxidation of the resultant alcohol provided ketone **111**. At this stage, the stereochemistry of the C27 stereogenic center was confirmed by an NOE experiment as shown. After a number of experiments, we found that the C26 methyl group could be introduced in a stereoselective manner by treatment of **111** with MeLi (1.2 equiv) in THF at −78 °C to room temperature. The desired alcohol **112** was isolated in 97% yield with an approximately 10:1 diastereoselectivity under these conditions, and the stereochemistry of the C26 stereogenic center was established by an NOE experiment as shown. Fortunately, the minor diastereomer could be removed by flash chromatography on silica gel. Tertiary alcohol **112** was converted to primary alcohol **113** via a standard, six-step sequence. This was iodinated and then treated with a base to furnish the DE-ring exocyclic enol ether **95**.

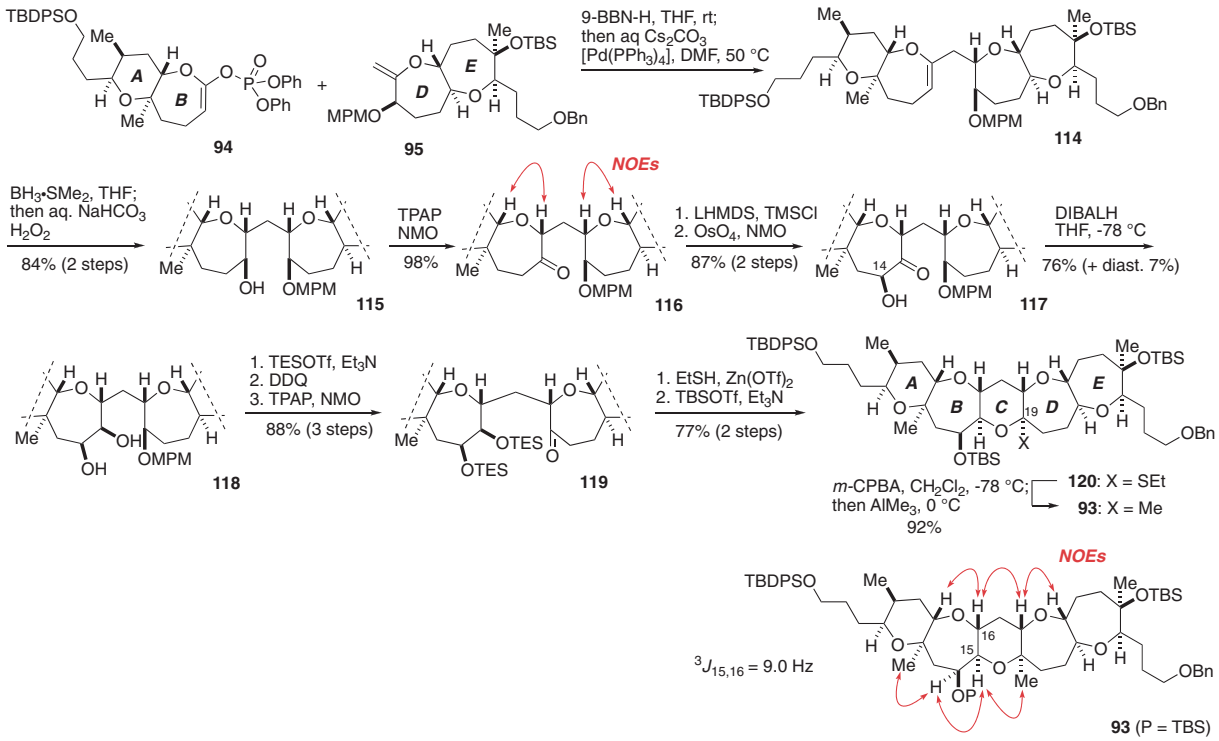


Figure 14. Convergent synthesis of the pentacyclic polyether core **93** of the proposed structure of brevenal.

3.5 Construction of the Pentacyclic Polyether Core. Having successfully synthesized the two key intermediates, we then investigated their assembly and formation of the C-ring (Figure 14). Stereoselective hydroboration of exocyclic enol ether **95** with 9-BBN-H proceeded smoothly to generate an alkylborane, which was in situ reacted with enol phosphate **94** in the presence of $[Pd(PPh_3)_4]$ catalyst and aqueous Cs_2CO_3 in THF/DMF at 50 °C. The resultant cross-coupled product **114** was stereoselectively hydroborated with $BH_3 \cdot SMe_2$ to afford, after alkaline oxidative workup, alcohol **115** as a single stereoisomer. TPAP/NMO oxidation of **115** gave ketone **116**, whose relative stereochemistry was established by NOE experiments as shown. Treatment of **116** with LHMDS in the presence of TMSCl gave an enol silane, which was dihydroxylated with OsO_4/NMO[66] to afford α-hydroxy ketone **117** as a single stereoisomer. The C14 hydroxy group was thus installed in a stereocontrolled manner. After extensive investigations, we found that reduction of **117** proceeded in a satisfactory diastereoselectivity (ca. 10:1) when **117** was reacted with DIBALH in THF at −78 °C. The desired diol **118** was isolated in 76% yield along with the undesired epimer in 7% yield under these conditions. The relative stereochemistry of **118** was confirmed by NOE experiments on a cyclopentylidene acetal derivative (not shown). Silylation, cleavage of the MPM group, and oxidation of the resultant alcohol gave ketone **119**. Exposure of **119** to $Zn(OTf)_2$ in THF/EtSH at room temperature resulted in a loss of the TES groups and concomitant mixed thioacetalization to deliver mixed thioacetal **120** in 77% yield. After silylation of the C14 hydroxy group as its TBS ether, the C19 methyl group was stereoselectively introduced by reacting **120** with *m*-CPBA in CH_2Cl_2 at −78 °C and then with excess $AlMe_3$,[44] leading to the pentacyclic ether **93** in 92% yield as a single stereoisomer. This one-pot procedure was crucial for the success, as all attempts to isolate the intermediary sulfone or sulfoxide met with failure, giving only the corresponding hemiacetal that arose from hydrolysis. The relative stereochemistry of **93** was unequivocally established on the basis of NOE experiments and $^3J_{H,H}$ analysis as shown.

3.6 Completion of the Total Synthesis of the Proposed Structure 91 of (−)-Brevenal. With securing the access to the pentacyclic polyether **93**, we proceeded to complete the total synthesis (Figure 15). After an eight-step standard sequence, the resultant alkyne **121** was functionalized via *syn*-selective silylcupration[67] to give vinylsilane **122** with good regioselectivity (ca. 9:1). Subsequent iododesilylation by the action of NIS[68] resulted in a partial isomerization of the double bond geometry, giving an approximately 6:1 mixture of (*E*)-vinyl iodide **123** and its (*Z*)-isomer, along with small amounts of regioisomers. Without separation of these isomers, this mixture was directly used in Stille coupling[69] with (*E*)-vinylstannane **124** under the influence of the $[Pd_2(dba)_3]/Ph_3As$ catalyst system and CuTC[70] as a co-catalyst in THF/DMSO (1:1) at room temperature. The desired (*E*,*E*)-diene **125** was isolated in 63% yield after purification by flash chromatography on silica gel. After standard protective group manipulations, the right-hand side chain was introduced in a stereoselective manner according to the procedure of Nicolaou.[71] Thus, oxidation, Wittig reaction, and subsequent peroxide treatment provided tetraene **127**. Global deprotection of the silyl groups and chemoselective oxidation with MnO_2 furnished synthetic **91**.

However, it was found that the ^1H and ^{13}C NMR spectra of synthetic **91** did not match those reported for natural product.

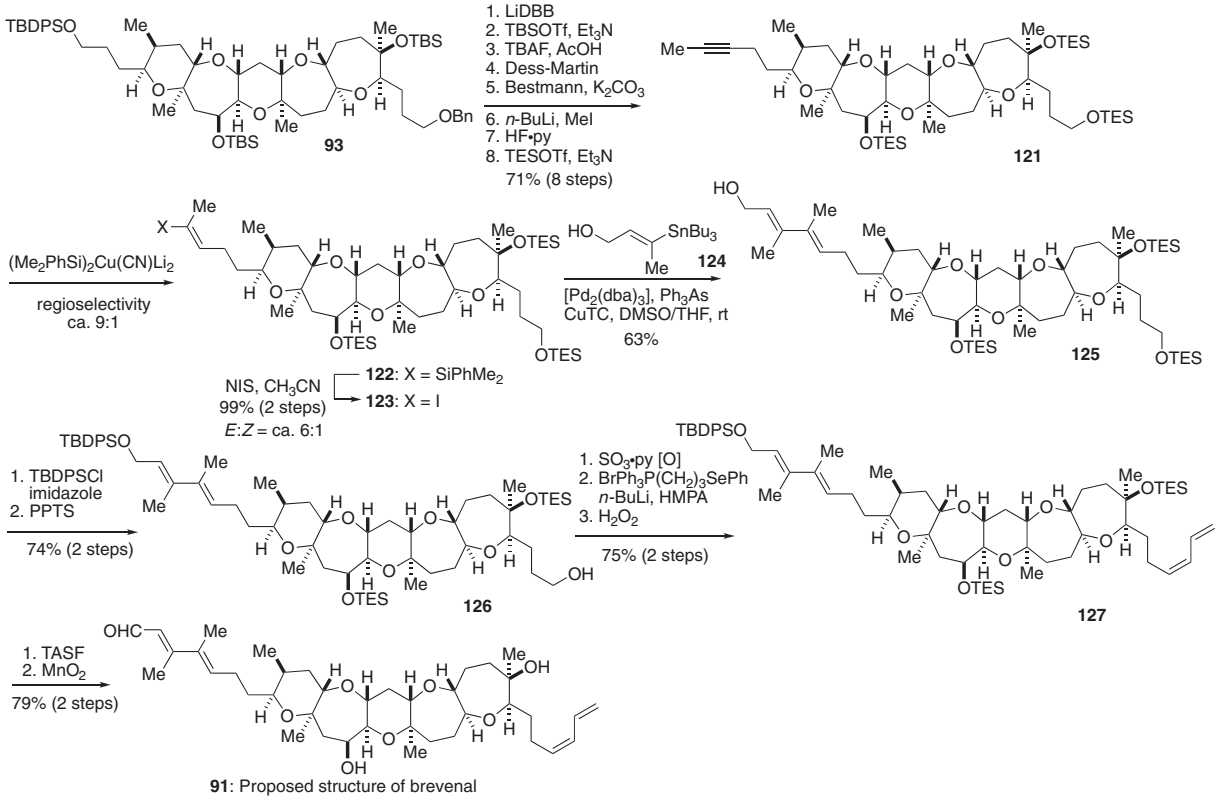


Figure 15. Completion of the total synthesis of the proposed structure **91** of brevenal.

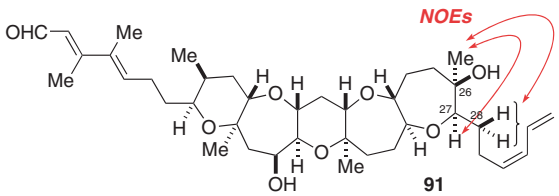


Figure 16. Diagnostic NOE correlations observed for synthetic **91**.

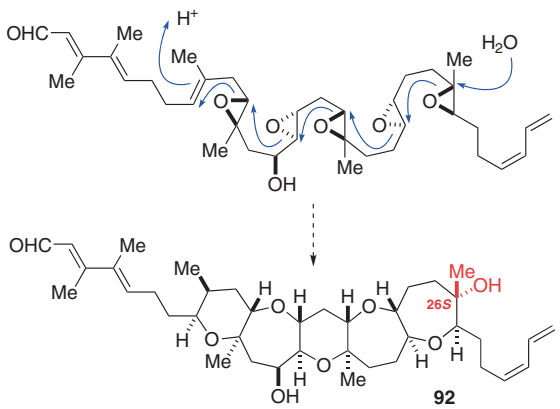


Figure 17. Plausible biosynthetic pathway for natural brevenal.

The gross structure of synthetic **91** was carefully assigned on the basis of extensive 2D NMR analysis, and the relative stereochemistry was established by a NOESY experiment. Although the planar structure of synthetic **91** was found to be identical to that of natural product on the basis of COSY, TOCSY, HSQC, and HMBC correlations as well as high-resolution mass spectroscopy, the ^{1}H and ^{13}C NMR chemical shift values of the E-ring domain of synthetic **91** differed subtly from those of natural product. In addition, in the NOESY spectrum of synthetic **91**, intense cross-peaks between the 26-methyl/27-H and 26-methyl/28-methylene were observed, while such correlations were not present in that of natural product (Figure 16). Thus, we thought that the stereochemistry of the C26 stereogenic center of the proposed structure **91** could have been incorrectly assigned. Accordingly, we revised the structure of (−)-brevenal as represented by **92**, which corresponds to the C26-epimer of the proposed structure (Figure 10). The revised structure **92** was also supported by the polyepoxide cyclization cascade pathway for the biosynthesis of marine polycyclic ether metabolites, proposed independently by Nakanishi and Shimizu (Figure 17).[58]

3.7 Total Synthesis of the Revised Structure 92 of (−)-Brevenal. We synthesized the DE-ring exocyclic enol ether **133** with the correct relative stereochemistry at the C26 stereogenic center from olefin **108** (Figure 18). Wacker oxidation of **108** under modified conditions[72] gave methyl ketone **128**. Desilylation followed by introduction of a β-alkoxyacrylate functionality afforded **129**, which on exposure to SmI_2 in THF/MeOH at room temperature provided lactone **130** in 57% yield along with hydroxy ester **131** in 37% yield. These products were individually reduced with $LiAlH_4$ (LAH) to give the same diol **132**. The relative stereochemistries of the newly generated stereogenic centers were established by NOE experiments on **130**. Conversion of diol **132** to the DE-ring exocyclic enol ether **133** and subsequent elaboration of the

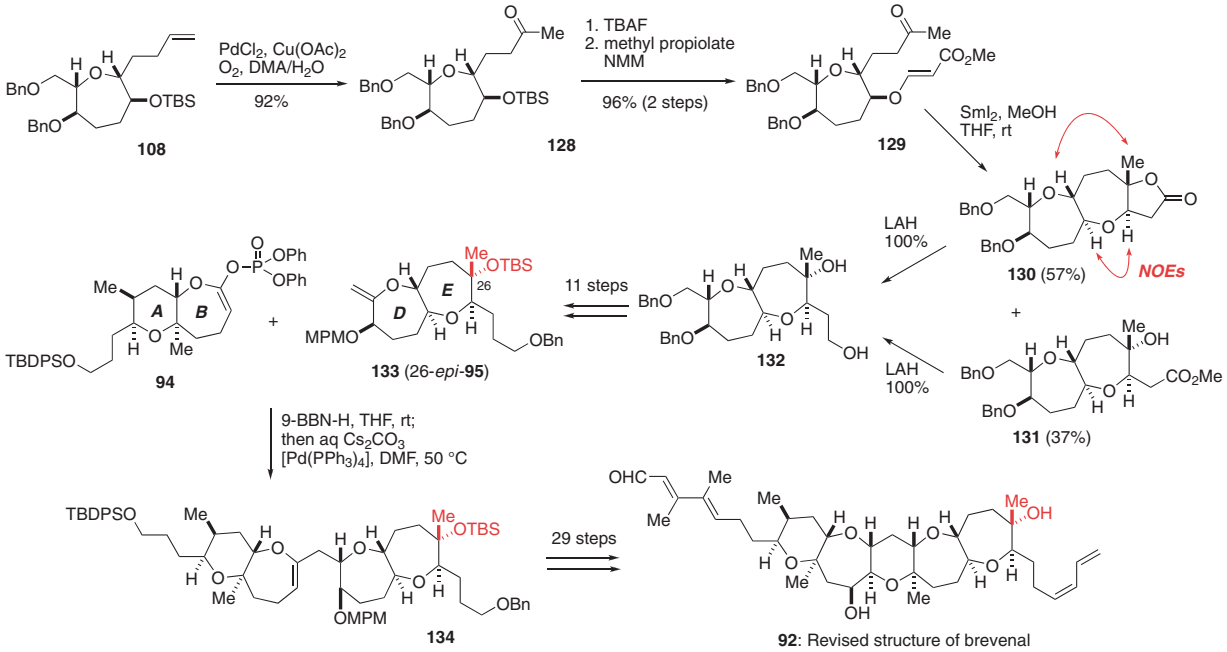


Figure 18. Completion of the total synthesis of the revised structure **92** of brevenal.

revised structure **92** were efficiently accomplished in the same way as described for the proposed structure **91**. Much to our delight, the spectroscopic data of synthetic **92**, including ^{1}H, ^{13}C NMR spectra and HRMS, were in full accordance with those reported for natural brevenal, thereby concluding that the correct structure of brevenal is the C26-epimer of the proposed structure **91**. Moreover, the specific rotation value of synthetic **92** matched exactly that reported for naturally occurring sample. Thus, the absolute stereostructure of (−)-brevenal was unequivocally determined to be the structure **92**.[59]

4. Total Synthesis of (+)-Neopeltolide

4.1 Background. Because of the highly oxygenated and stereochemically complex molecular architecture, marine macrolide natural products, the secondary metabolites of marine invertebrates, especially sponges, or their symbiotic bacteria, provide a plethora of opportunities for testing the versatility and applicability of newly developed organic reactions and strategies. In addition, numerous marine macrolide natural products have been shown to exhibit potent cytotoxicity or anti-proliferative activity against cancer cells, thereby representing a rich source of promising lead compounds for the development of anticancer drugs. Nevertheless, the availability of marine macrolide natural products is in most cases severely restricted, because they are often very minor metabolic constituents in marine organisms. As such, marine macrolide natural products represent attractive and formidable targets for synthetic organic chemists.[73]

(+)-Neopeltolide is a marine macrolide natural product isolated from a deep-water sponge of the family Neopeltidae, collected off the coast of Jamaica.[74] Its gross structure including the relative stereochemistry was proposed to be the structure **135** on the basis of extensive 2D NMR analysis (Figure 19). The structure of (+)-neopeltolide consists of a 14-membered macrolactone embedded with a 2,4,6-trisubstituted

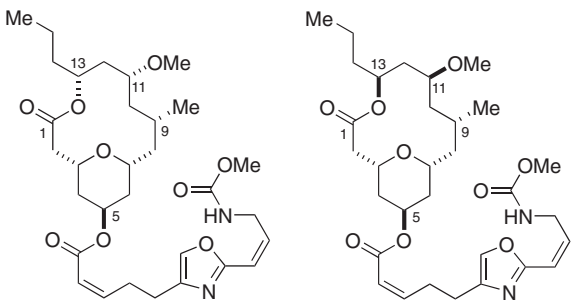


Figure 19. The proposed structure **135** and the correct structure **136** of (+)-neopeltolide.

tetrahydropyran ring and an oxazole-containing unsaturated side chain reminiscent of leucascandrolide A,[75] another marine macrolide natural product. Significantly, (+)-neopeltolide displays highly potent cell growth anti-proliferative activity against several cancer cell lines at nanomolar concentrations as well as antifungal activity against pathogenic yeast *Candida albicans*. The first total synthesis of (+)-neopeltolide was accomplished by Panek and co-workers, which led to reassignment of the relative stereochemistry of the proposed structure **135** and determination of the absolute stereostructure as represented by structure **136**.[76] Kozmin and co-workers reported that synthetic (±)-neopeltolide inhibits cytochrome bc_1 complex as the primary cellular target in mammalian cells and yeasts.[77] This finding may account for the potent anti-proliferative activity of (+)-neopeltolide. The synthetically challenging molecular structure coupled with intriguing biological activities renders this natural product a rewarding synthetic target for organic chemists.[78]

4.2 Synthesis Plan. We independently launched a program directed toward the total synthesis of (+)-neopeltolide (**136**) on

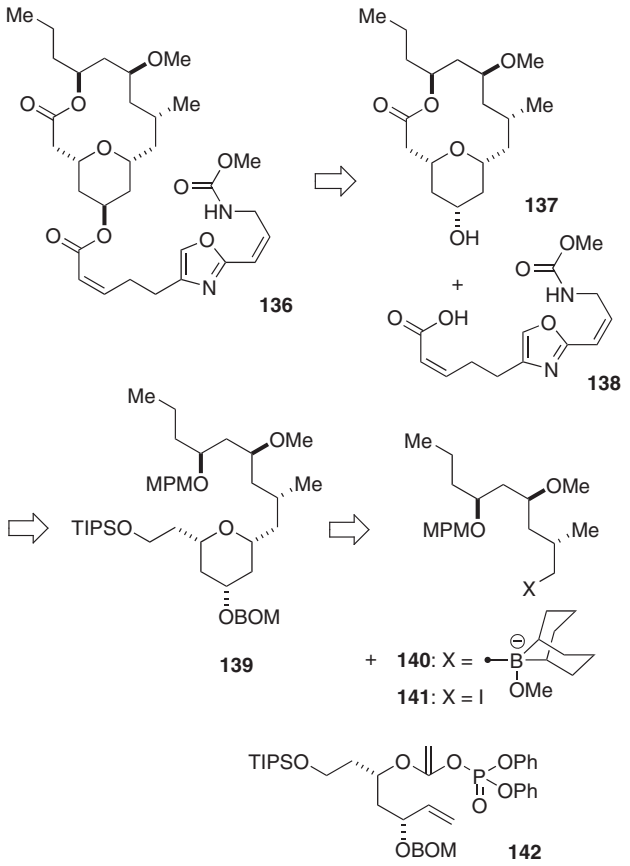


Figure 20. Synthesis plan toward (+)-neopeltolide.

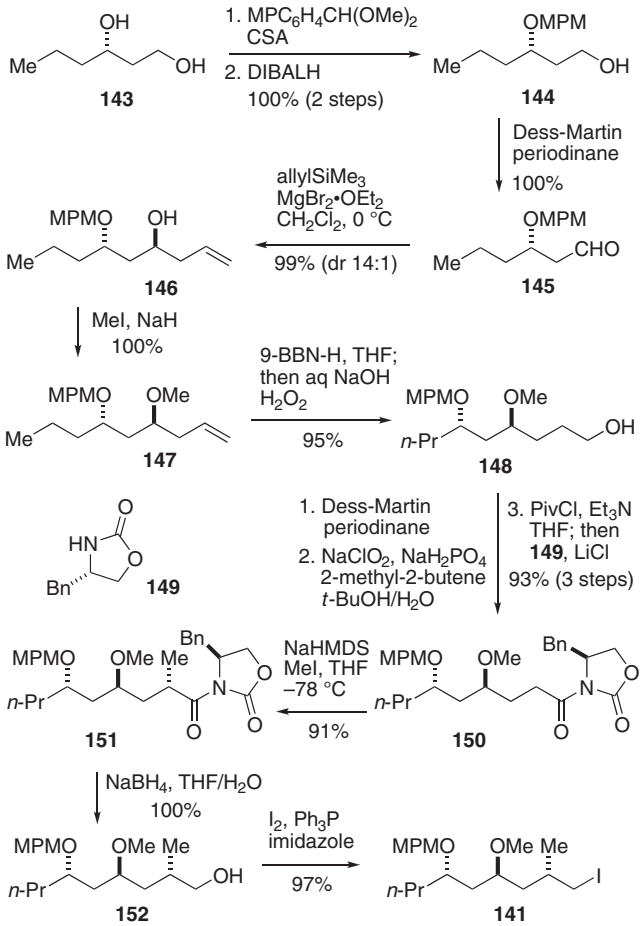


Figure 21. Synthesis of iodide **141**.

the basis of a convergent strategy that exploits Suzuki–Miyaura coupling, as summarized in Figure 20. We planned to assemble alcohol **137** with the oxazole-containing side chain **138** at a final stage of our total synthesis. The 14-membered macrolactone framework of **137** would be constructed via macrolactonization. We envisioned that the 2,4,6-trisubstituted tetrahydropyran **139** could be synthesized from alkylborate **140** and acyclic enol phosphate **142** in a convergent manner via a Suzuki–Miyaura coupling/ring-closing metathesis sequence.[79–81] Although there was a concern that intramolecular Heck reaction[82] of **142** might competitively take place by the action of a palladium catalyst and a base, our previous findings on a related substrate[83] suggested that it would be possible to couple **140** and **142** under appropriate conditions.

4.3 Synthesis of Iodide 141. The synthesis of iodide **141**, the precursor of alkylborate **140**, started with the known 1,3-diol **143**,[84] which was transformed into aldehyde **145** in a routine, three-step sequence (Figure 21). The C11 stereogenic center was established by chelation-controlled allylation of **145** (allyltrimethylsilane, $MgBr_2 \cdot OEt_2$, CH_2Cl_2, 0 °C). The desired homoallylic alcohol **146** was isolated in 99% yield with ca. 14:1 diastereoselectivity. After methylation of **146** to give methyl ether **147** quantitatively, hydroboration of the terminal alkene provided alcohol **148**. A two-stage oxidation followed by condensation with (*S*)-4-benzyl-2-oxazolidinone (**149**)[85] afforded imide **150**, whose asymmetric alkylation under Evans conditions[86] led to methylated product **151** as a single stereoisomer. After reductive removal of the chiral auxiliary,[62] iodination of the derived alcohol **152** furnished iodide **141**.

4.4 Synthesis of Enol Phosphate 142. The synthesis of enol phosphate **142** commenced with asymmetric allylation of aldehyde **153**, derived from 1,3-propanediol in two steps, according to the Keck procedure[87] (Figure 22). This afforded homoallylic alcohol **154** in 93% yield with greater than 95% ee. After protection of the resultant alcohol as its MPM ether to give **155**, the terminal alkene was homologated via olefin cross-metathesis[88] to deliver enoate **156**. After reduction of **156**, the derived allylic alcohol **157** was epoxidized under Sharpless conditions to give epoxy alcohol **158** as a single stereoisomer, which was iodinated and then reduced with zinc to provide allylic alcohol **159**. Protection of **159** as its BOM ether, cleavage of the MPM ether, and subsequent acylation afforded acetate **160**, which on treatment with KHMDS/$(PhO)_2P(O)Cl$ delivered enol phosphate **142**.

4.5 Construction of the 2,4,6-Trisubstituted Tetrahydropyran Subunit. With two key fragments **141** and **142** available, we proceeded to construct the 2,4,6-trisubstituted tetrahydropyran subunit **139**, as illustrated in Figure 23. Treatment of iodide **141** with *t*-BuLi in the presence of *B*-MeO-9-BBN generated alkylborate **140**,[89] which was in situ reacted with enol phosphate **142** under the influence of $[Pd(PPh_3)_4]$ catalyst and aqueous Cs_2CO_3 in DMF at room temperature. Subsequent ring-closing metathesis of the derived

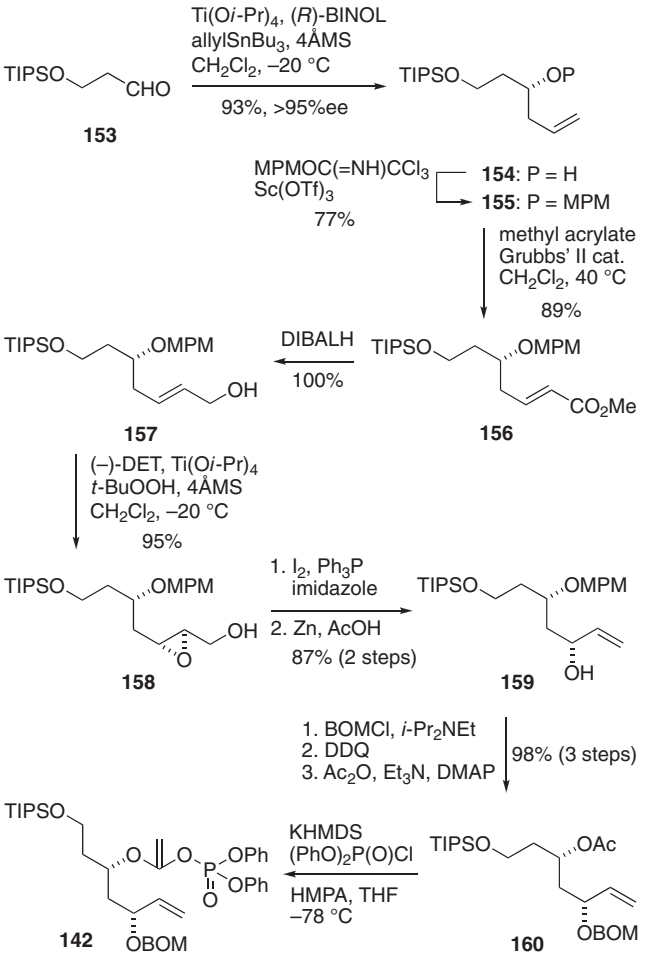


Figure 22. Synthesis of enol phosphate **142**.

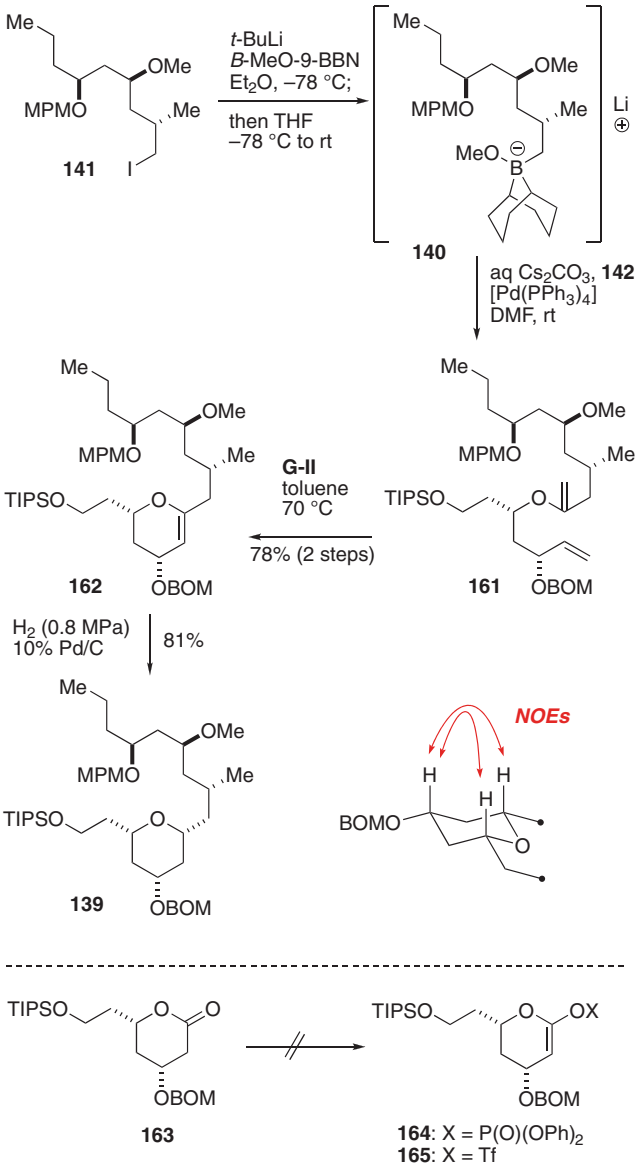


Figure 23. Elaboration of 2,4,6-trisubstituted tetrahydropyran **139**.

diene **161** by the action of Grubbs second-generation catalyst (toluene, 70 °C) afforded dihydropyran **162** in 78% overall yield from iodide **141**. We found it important to perform the Suzuki–Miyaura coupling at room temperature, since acyclic enol phosphate **142** was unstable under the alkaline conditions and readily underwent hydrolysis at higher temperatures. Significantly, the intermolecular Suzuki–Miyaura coupling of **140** and **142** predominated over the possible intramolecular Heck reaction of **142**. In contrast, our attempts at preparing lactone-derived enol phosphate **164** or the corresponding triflate **165** were completely unrewarding, since the parent lactone **163** was found to decompose instantaneously on treatment with a base (KHMDS, THF, −78 °C). This finding clearly demonstrates that our Suzuki–Miyaura coupling/ring-closing metathesis sequence from acyclic enol phosphates represents a powerful alternative to Suzuki–Miyaura coupling of lactone-derived enol phosphates or triflates. Hydrogenation of **162** proceeded with complete stereoselectively to furnish 2,4,6-trisubstituted tetrahydropyran **139** as a single stereoisomer. The stereochemistry of the tetrahydropyran ring of **139** was established by NOE experiments as shown.

4.6 Completion of the Total Synthesis of (+)-Neopeltolide. We finally arrived at the target molecule, (+)-neopeltolide **136**, as summarized in Figure 24. A four-step sequence including desilylation, oxidation, and esterification elaborated tetrahydropyran **139** to methyl ester **167** in high overall yield. Deprotection of the MPM group followed by saponification[90] gave hydroxy acid **168**. The 14-membered macrolactone framework was successfully forged via Yamaguchi lactonization, providing **169**, which upon hydrogenolysis of the BOM group afforded alcohol **137** quantitatively. Finally, coupling of **137** with the known acid **138**[91] under Mitsunobu conditions[92] furnished synthetic (+)-neopeltolide **136** in 61% yield. The spectroscopic data and specific rotation value of our synthetic material were in full accordance with those reported for natural product.[93]

5. Concluding Remarks

In this Account, we described the total synthesis of structurally complex oxacyclic natural products by exploiting Suzuki–Miyaura coupling of enol phosphates. We developed new synthetic strategies for the construction of oxacycles by

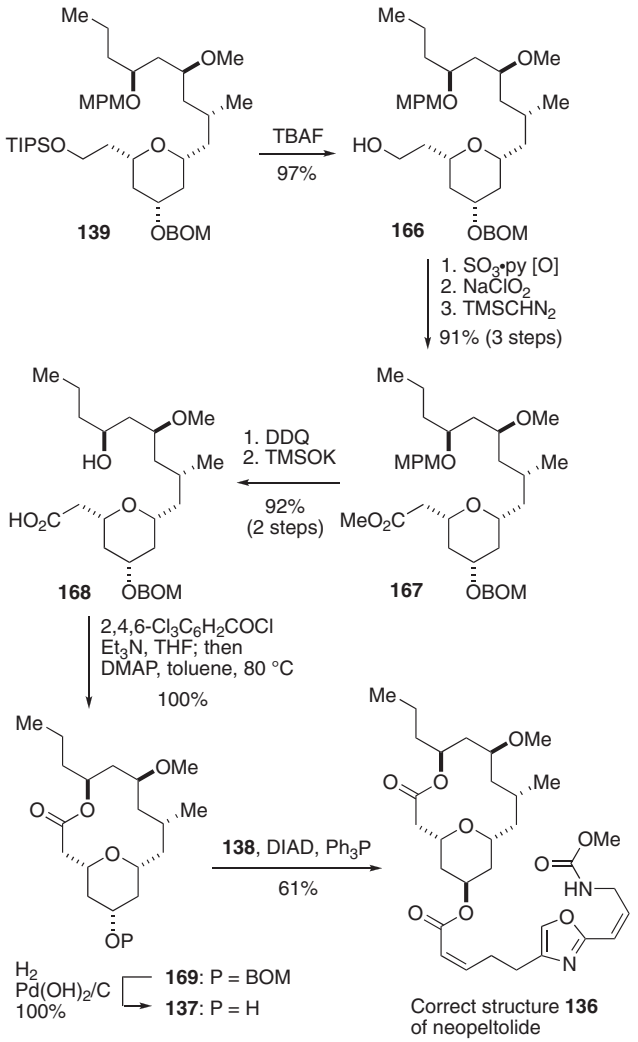


Figure 24. Completion of the total synthesis of (+)-neopeltolide **136**.

exploiting the unique reactivity of enol phosphates in palladium-catalyzed reactions, which enabled us to build up complex naturally occurring molecules in an efficient manner.[83,94] Total synthesis of (−)-gambierol has been accomplished for the first time, which realized material supply in ample quantities for extensive biological investigations, including elucidation of its molecular target in mouse taste cells and establishment of its structure–activity relationships. Total synthesis of (−)-brevenal has also been achieved for the first time, which culminated in the structure revision and determination of the absolute configuration of the natural product. Our strategy for the convergent synthesis of *trans*-fused polycyclic ethers has also been utilized in the synthesis of ciguatoxins,[95] gymnocin A,[96] gambieric acids,[97] brevisin,[98] and maitotoxin,[99] thus demonstrating its generality and feasibility. Total synthesis of (+)-neopeltolide has been completed on the basis of our newly developed Suzuki–Miyaura coupling/ring-closing metathesis strategy. Importantly, our synthetic efforts have been fruitful in paving the way to elucidate structure–activity relationships and biological mode-of-actions of these biologically intriguing molecules.[52,54,93b]

However, at the same time, our synthetic strategies described here still require an impractical number of chemical transformations for gram-scale preparation of complex oxacyclic natural products. Thus, we are now keen to develop innovative synthetic strategies that realize more efficient and practical synthesis of complex molecules by pursing chemo-, regio-, and stereoselectivities. In this context, we have very recently accomplished significantly improved total syntheses of (−)-brevenal[100] and (+)-neopeltolide.[101] Further studies along this line are currently ongoing in our laboratory.

This work was performed at the University of Tokyo and Tohoku University. I would like to express my sincere gratitude to Professor Makoto Sasaki (Tohoku University) for his generous support throughout this work. I am grateful to Professor Kazuo Tachibana (the University of Tokyo), who guided me into the chemistry of natural products during my early career. I very much appreciate all of my collaborators, particularly Ms. Noriko Kainuma, Dr. Makoto Ebine, Mr. Shinya Naito, Ms. Tomomi Goto, and Ms. Asami Saito, who made significant contributions to the work described in this Account.

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