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# Convergent Total Syntheses of Gambierol and 16-*epi*-Gambierol and Their Biological Activities

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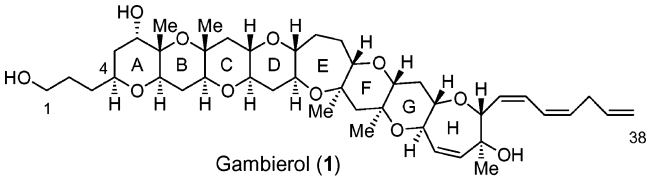
***Abstract:*** The convergent total syntheses of gambierol (**1**) and 16-*epi*-gambierol (**2**) have been achieved. The ABC and FGH ring segments **4** and **5** were prepared from known compounds **6** and **13**, respectively, by linear manners. The fragments prepared were connected by our own synthetic strategy including the intramolecular allylation of α-acetoxy ether followed by ring-closing metathesis to furnish the octacyclic ether **3**. The diiodoalkene **45**, prepared from **3**, was converted to the *Z*-iodoalkene **50** via a novel and stereoselective hydrogenolysis followed by deprotection. Construction of the triene side chain was performed by the modified Stille coupling of **50** with the *Z*-vinylic stannane **41** to afford **1**. The similar transformations were carried out on the epimeric octacycle **34** to give **2**, which showed no toxicity against mice at the concentration of 14 mg/kg.

## Introduction

In recent years there has been an explosion of interest in biologically active natural products of marine origin.[1] Due to their structural novelty and toxicity, polycyclic ethers are particularly attractive targets for synthetic chemists.[2] Gambierol (**1**), a potent neurotoxin isolated from the cultured cells of *Gambierdiscus toxicus*, has 8 ether rings and 18 stereogenic centers (Figure 1).[3] The compound shows toxicity against mice ($LD_{50}$ 50 μg/kg), and the symptoms resemble those caused by ciguatoxins, inferring the possibility that it is also implicated in ciguatera poisoning. The unique structural features have attracted the attention of synthetic chemists, and a number of strategies have been investigated.[4] Soon after the first total synthesis of **1** was accomplished by Sasaki, Tachibana, and co-workers,[5] we also communicated the total synthesis of **1**.[6] In this contribution, we report full details of the convergent total synthesis of gambierol (**1**) together with the synthesis of 16-*epi*-gambierol (**2**), based on our own synthetic methodology, and the biological activities of **1** and **2**.



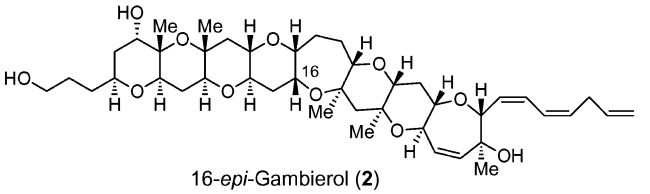




***Figure 1.*** Structures of gambierol (**1**) and 16-*epi*-gambierol (**2**).

## Results and Discussion

**Retrosynthetic Analysis**. A brief retrosynthetic analysis of **1** is illustrated in Scheme 1. According to our preliminary study for the synthesis of the H ring moiety, the triene side chain

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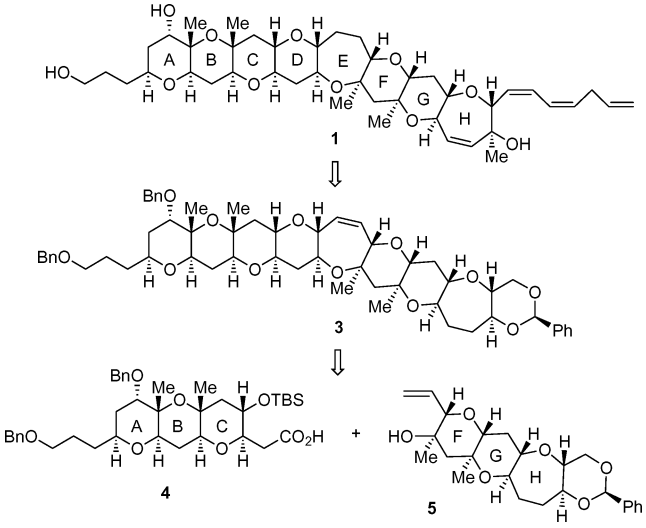
***Scheme 1.*** Retrosynthetic Analysis of Gambierol (**1**)

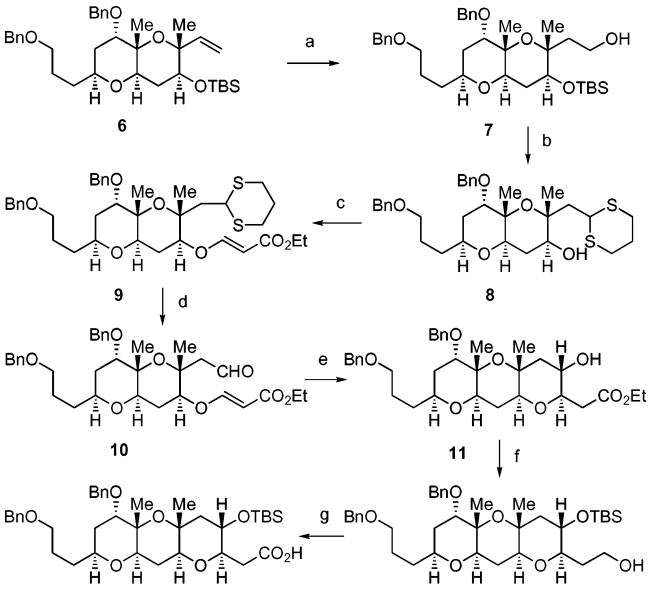


would be constructed by a modified Stille coupling at a late stage. Recently, we developed a convergent method for the synthesis of polycyclic ether frameworks via the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis.[4i,l] Upon the basis of this methodology, the key intermediate, octacyclic ether **3**, can be retrosynthetically broken down into the ABC and FGH segments, **4** and **5**.

**Synthesis of the ABC Ring Segment 4.** Synthesis of the ABC ring segment **4** was started from the known bicycle **6**,[4h] corresponding to the AB ring system (Scheme 2). Hydroboration of **6** gave the alcohol **7** in 95% yield. TEMPO oxidation of **7**,[7] protection of the resulting aldehyde as a dithio acetal, and desilylation with TBAF afforded **8** in 86% yield. Reaction with ethyl propiolate and *N*-methylmorpholine gave the acrylate **9** in 94% yield. The dithio acetal protection of **9** was removed by MeI in wet acetonitrile to give the aldehyde **10** in 94% yield. Construction of the C ring moiety was performed by using Nakata protocol. Thus, treatment of **10** with $SmI_2$ in the presence of MeOH provided the tricyclic compound **11** as a single stereoisomer in 98% yield.[8] TBS protection followed by $LiAlH_4$ reduction of the ester group gave the alcohol **12**, which was oxidized to the carboxylic acid **4** in quantitative yield.

**Synthesis of the FGH Ring Segment 5.** Synthesis of the FGH ring segment **5** is shown in Scheme 3. Reduction of the known ester **13**[4e] having 1,3-diaxial methyl groups with $LiAlH_4$ followed by protection with TBSOTf/2,6-lutidine gave the bissilyl ether **14** in quantitative yield. Hydrolysis of the benzylidene acetal followed by selective tosylation of the primary alcohol afforded **16** in 84% yield. Treatment of **16** with an excess amount of allylmagnesium bromide in the presence of CuBr gave the alkylated product **17** in 95% yield. Ozonolysis of the olefin, reduction with $NaBH_4$, and selective protection of the

***Scheme 2.*** Synthesis of the ABC Ring Segment **4**[a]



[a] (a) $(c\text{-Hex})_2BH$, THF, 0 °C, then $H_2O_2$, NaOH, 95%; (b) (i) TEMPO, NaClO, KBr, $NaHCO_3$, $CH_2Cl_2-H_2O$, 0 °C; (ii) 1,3-propanedithiol, $BF_3.OEt_2$, $CH_2Cl_2$, −78 to 0 °C; (iii) TBAF, THF, rt, 86% (3 steps); (c) ethyl propiolate, NMM, $CH_2Cl_2$, rt, 94%; (d) MeI, $NaHCO_3$, $CH_3CN-H_2O$, 50 °C, 94%; (e) $SmI_2$, MeOH, THF, 0 °C, 98%; (f) (i) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C (ii) $LiAlH_4$, ether, 0 °C, 92% (2 steps); (g) (i) TEMPO, NaClO, KBr, $NaHCO_3$, $CH_2Cl_2-H_2O$, 0 °C; (ii) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4$, *t*-BuOH−THF−$H_2O$, rt, quant (2 steps).

primary alcohol with PivCl/pyridine gave **18** in 98% yield. Acid-catalyzed acetal formation with the γ-methoxyallylstannane **19** followed by acetal cleavage with TMSI/HMDS furnished the allylic stannane **20** in 81% yield.[9] Reductive removal of the Piv protection with DIBALH gave the alcohol **21**, which was oxidized with $SO_3$·py/DMSO/$Et_3N$ to afford the aldehyde **22** in 97% yield. Cyclization of **22** mediated by $BF_3$·$OEt_2$ gave the 6,6,7-tricyclic compound **23** in 99% yield as a single stereoisomer.[10] Ozonolysis of the olefin followed by reductive workup, protection of the resulting 1,3-diol as a benzylidene acetal, and selective desilylation of the primary alcohol furnished **24** in 86% yield. Treatment of **24** with 2-nitrophenyl selenocyanate/$Bu_3P$ followed by oxidative work up gave the alkene **25** in 97% yield.[11] Treatment of **25** with TBAF afforded the FGH ring segment **5** in quantitative yield.

**Construction of the Octacyclic Ether Framework.** The next task of the total synthesis was the construction of the octacyclic framework. The carboxylic acid **4** and the alcohol **5** were connected by Yamaguchi conditions to give the ester **26** in 94% yield (Scheme 4).[12] A series of reactions including desilylation with TBAF, acid-catalyzed acetal formation with **19**, and acetal cleavage with TMSI/HMDS furnished the allylic stannane **28** in 77% yield. The ester **28** was converted to the α-acetoxy ether **29** via the Rychnovsky protocol. Thus, partial reduction of **28** with DIBALH, followed by treatment of the resulting aluminum

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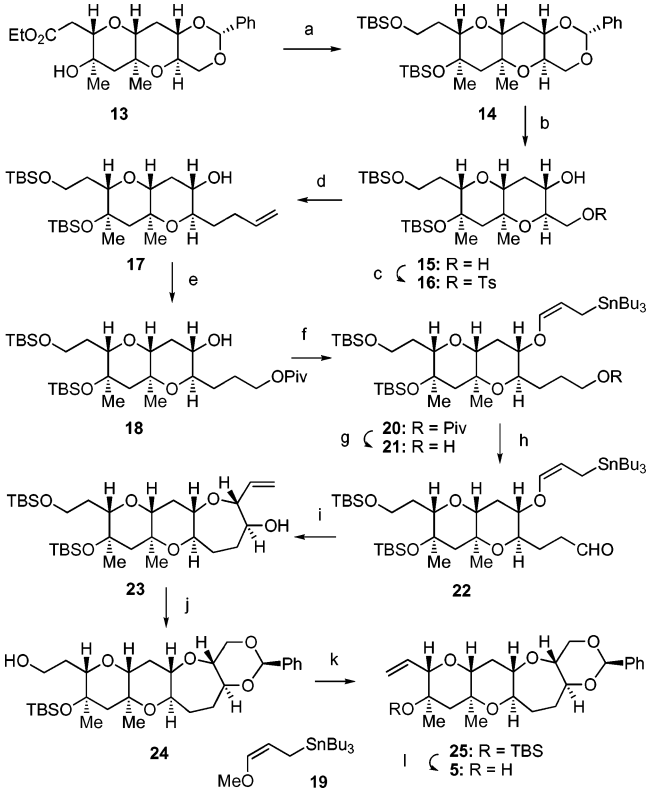
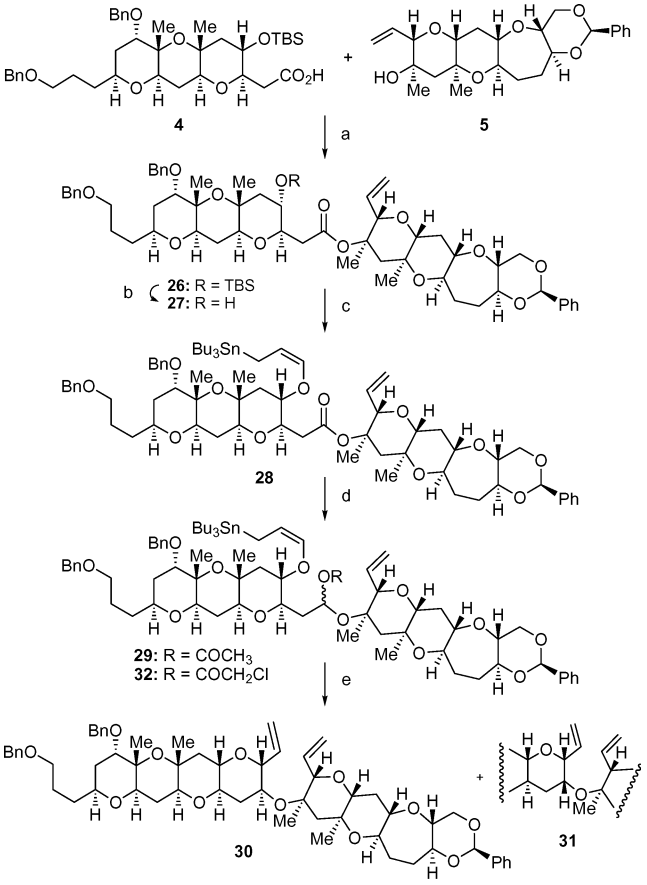
***Scheme 3.*** Synthesis of the FGH Ring Segment **5**[a]



[a] (a) (i) $LiAlH_4$, ether, 0 °C; (ii) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C to rt, 100% (2 steps); (b) $H_2$, $Pd(OH)_2$−C, EtOAc, rt, 100%; (c) TsCl, $Et_3N$, $CH_2Cl_2$, reflux, 84%; (d) allylmagnesium bromide, CuBr, THF, −20 °C to rt, 95%; (e) (i) $O_3$, MeOH, −78 °C, then $Me_2S$, $NaBH_4$; (ii) PivCl, pyridine, $CH_2Cl_2$, 0 °C to rt, 98% (2 steps); (f) (i) **19**, CSA, $CH_2Cl_2$, rt, 99%; (ii) HMDS, TMSI, $CH_2Cl_2$, 0 °C, 82%; (g) DIBALH, $CH_2Cl_2$, −78 °C, 100%; (h) $SO_3$·py, DMSO, $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 97%; (i) $BF_3$·$OEt_2$, $CH_2Cl_2$, −78 °C, 99%; (j) (i) $O_3$, $CH_2Cl_2$−MeOH, −78 °C, then $NaBH_4$; (ii) $PhCH(OMe)_2$, CSA, $CH_2Cl_2$, 0 °C; (iii) AcOH, THF−$H_2O$, 30 °C, 86% (3 steps); (k) 2-nitrophenyl selenocyanate, $PBu_3$, THF, rt, then $H_2O_2$, $NaHCO_3$, 40 °C, 97%; (l) TBAF, THF, reflux, 100%.

hemiacetal with $Ac_2O$/pyridine/DMAP gave **29** as a 3:2 inseparable mixture of diastereoisomers in 78% yield.[13] The cyclization precursor **29** was then treated with $MgBr_2$·$OEt_2$ in $CH_2Cl_2$ to afford a mixture of the desired product **30** and its epimer **31** in 61% yield. Unfortunately, the undesired stereoisomer **31** was the major component. The ratio of **30** and **31** was 36:64. After several unfruitful attempts, we found the conditions giving the desired product predominantly. Treatment of the α-chloroacetoxy ether **32**, prepared from **28** via DIBALH reduction followed by trapping with $(CH_2ClCO)_2O$/pyridine/DMAP, with $BF_3$·$OEt_2$ in $CH_3CN$−$CH_2Cl_2$ (20:1) furnished **30** and **31** in the ratio of 64:36 in 87% yield. Although the reason is not clear, probably, the greater leaving ability of chloroacetoxy group, in comparison with that of the acetoxy group, would drive the reaction to proceed through $S_N1$ pathway giving the desired isomer **30** predominantly. It should be noted that the use of chloroacetyl group improved not only the cyclization step but also preparation of the substrate. The reaction time required for the chloroacetylation was decreased to 1 h in comparison to 12 h for the acetylation, and the yield was improved to 88% from 78%.

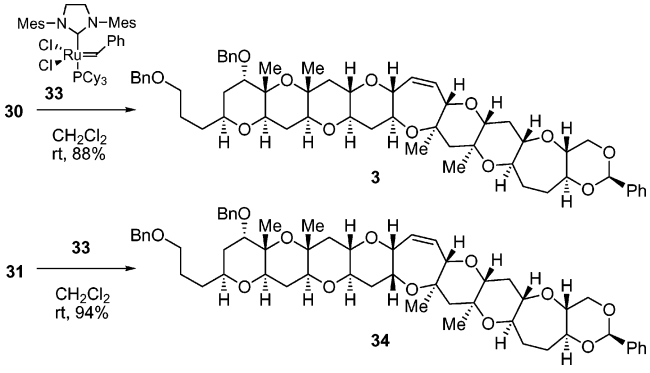
***Scheme 4.*** Coupling of the Segments **4** and **5**[a]



| R | Lewis acid | **30** : **31** | yield |
|---|---|---|---|
| acetyl (**29**) | $MgBr_2$·$OEt_2$ | 36 : 64 | 61% |
| chloroacetyl (**32**) | $BF_3$·$OEt_2$ | 64 : 36 | 87% |

[a] (a) 2,4,6-Trichlorobenzoyl chloride, $Et_3N$, THF, 40 °C, then **5**, DMAP, toluene, 40 °C, 90%; (b) TBAF, THF, rt 99%; (c) (i) **19**, CSA, $CH_2Cl_2$, rt; (ii) HMDS, TMSI, $CH_2Cl_2$, 0 °C, 78% (2 steps); (d) DIBALH, $CH_2Cl_2$, −78 °C, then $R_2O$, DMAP, pyridne, −78 °C to rt, 78% for **29**, 88% for **32**; (e) $MgBr_2$·$OEt_2$, MS4A, $CH_2Cl_2$, rt, or $BF_3$·$OEt_2$, MS4A, $CH_3CN$−$CH_2Cl_2$ (20:1), −40 to 0 °C.

***Scheme 5.*** Ring-closing Metathesis of **30** and **31**



The diene **30** obtained was subjected to ring-closing metathesis using the second-generation Grubbs catalyst **33**,[14] leading to the octacyclic ether **3** in 88% yield (Scheme 5). Similarly, the stereoisomer **31** was converted to **34** in 94% yield. The stereochemistries of **3** and **34** were determined on the basis of

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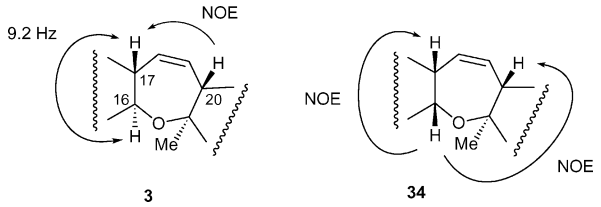
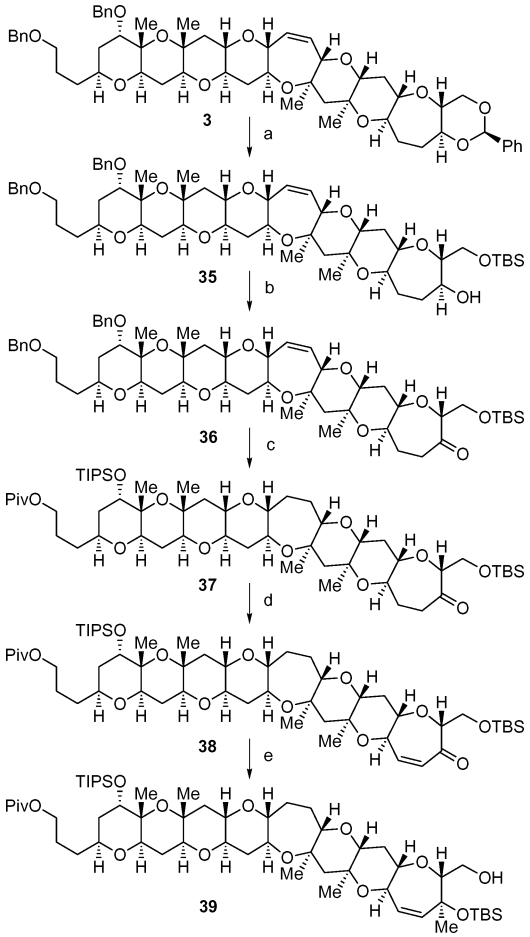



***Figure 2.*** Structure determination of **3** and **34**.

***Scheme 6*** [a]

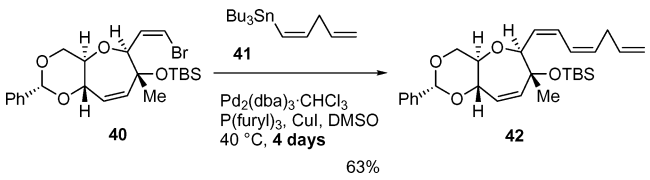



[a] (a) (i) CSA, $CH_2Cl_2$−MeOH, 30 °C; (ii) TBSCl, imidazole, $CH_2Cl_2$, 0 °C, 80% (2 steps); (b) TPAP, NMO, MS4A, $CH_2Cl_2$, rt, 96%; (c) (i) $H_2$, Pd−C, EtOAc, rt; (ii) $H_2$, $Pd(OH)_2$−C, EtOAc, rt; (iii) PivCl, DMAP, $CH_2Cl_2$, rt; (iv) TIPSOTf, 2,6-lutidine, DMF, 65 °C, 80% (4 steps); (d) (i) LiHMDS, TMSCl, $Et_3N$, THF, −78 °C; (ii) $Pd(OAc)_2$, $CH_3CN$, rt, 92% (2 steps); (e) (i) MeMgI, toluene, −78 °C; (ii) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, rt; (iii) CSA, $CH_2Cl_2$−MeOH, 0 °C, 82% (3 steps).

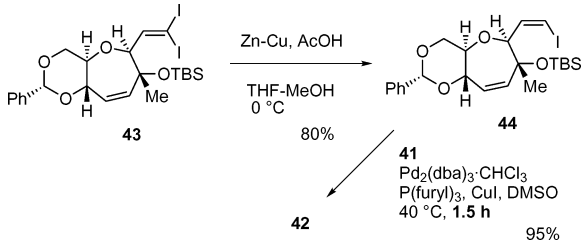
$^1$H NMR coupling constant and NOE experiments as shown in Figure 2.

**Modification of the H Ring Moiety.** Hydrolysis of the benzylidene acetal of **3** followed by selective protection of the primary alcohol gave **35** in 80% yield (Scheme 6). TPAP oxidation of the secondary alcohol **35** gave the ketone **36** in 96% yield. Hydrogenation of **36** followed by debenzylation gave the saturated diol. The primary and secondary alcohols were protected by Piv and TIPS groups, respectively, to afford **37** in 80% yield. Treatment of **37** with LiHMDS/TMSCl/$Et_3N$ gave the corresponding enol silyl ether,[5] which was subjected to dehydrosilylation with $Pd(OAc)_2$ to afford the enone **38** in 92% overall yield.[15] Stereoselective introduction of a methyl group was carried out using MeMgI in toluene to give the tertiary alcohol as a single stereoisomer.[16] TBS protection and subsequent selective deprotection of the primary silyloxy group afforded **39** in 82% yield.

***Scheme 7***




***Scheme 8***




**Model Studies for the Synthesis of the Triene Side Chain.** As well as the synthesis of the octacyclic ether framework, the stereoselective construction of the triene side chain was one of the challenging problems inherent in the total synthesis of gambierol. We chose the Stille coupling reaction[17] as a possible route to the triene side chain, since we had established a rather easy synthetic method for the *Z*-vinylstannane **41**.[4c,18] For a preliminary study, the *Z*-bromoalkene **40**, prepared from the corresponding dibromoalkene by the Uenishi procedure,[19] was subjected to the coupling with the *Z*-vinyl stannane **41** under the modified Stille conditions[20] to afford the triene **42** as a single stereoisomer in 63% yield (Scheme 7).[4c] Although **42** was obtained selectively in an allowable yield, the reaction was very slow. A significant amount of the starting material **40** remained even after 4 days. It was easily expected that the reaction of the bulky substrate having an octacyclic ether skeleton would be much slower. This problem prompted us to develop an efficient method for the construction of the triene side chain.[21] After several unfruitful attempts, we found that the reduction of the diiodoalkene **43** with Zn−Cu couple and acetic acid gave the *Z*-iodoalkene **44** as the sole product in 80% yield (Scheme 8).[22,23] As expected, the iodoalkene **44** showed higher reactivity, and the coupling reaction with **41** was finished within 1.5 h to afford **42** in 95% yield. None of the other olefinic isomers was detected in this reaction.

**Completion of the Total Synthesis of Gambierol.** Encouraged by the results obtained above, we faced up to the final

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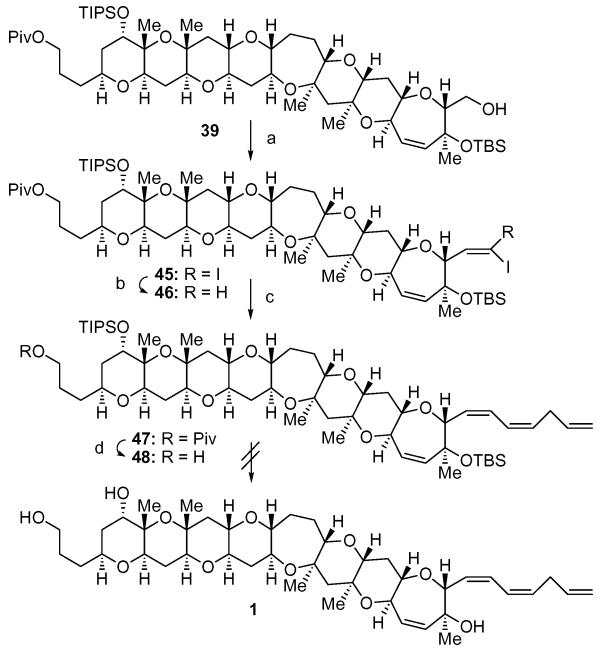
(21) Sasaki found an effective catalyst system for the coupling of *Z*-bromoalkenes, see ref 5.
(22) The palladium-catalyzed hydrogenolysis of diiodoalkenes with $Bu_3SnH$ was not selective, see ref 19c.
(23) The iodoolefination of the corresponding aldehyde using Wittig reagent gave a mixture of stereoisomers.

***Scheme 9*** [a]



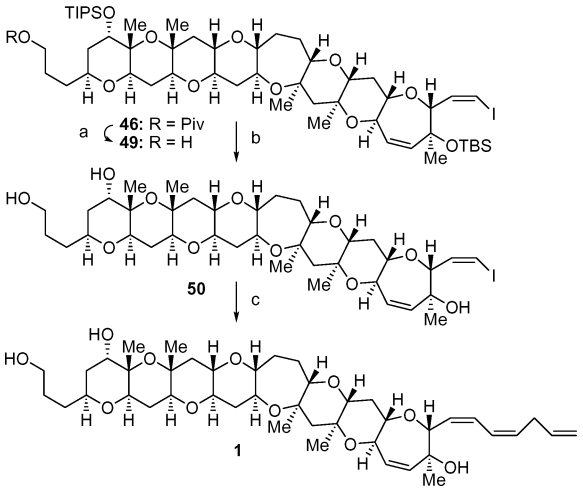

[a] (a) (i) PCC, MS4A, $CH_2Cl_2$, rt; (ii) $Cl_4$, $PPh_3$, $CH_2Cl_2$, 0 °C, 92% (2 steps); (b) Zn−Cu, AcOH, THF−MeOH, 0 °C; (c) **41**, $Pd_2(dba)_3$·$CHCl_3$, P(furyl)$_3$, CuI, DMSO, 40 °C, quant (2 steps); (d) DIBALH, $CH_2Cl_2$, −78 °C.

stage of the total synthesis. Thus, PCC oxidation of **39** followed by treatment of the resulting aldehyde with $CI_4$ and $PPh_3$ gave the diiodoalkene **45** in 92% yield (Scheme 9).[24] Stereoselective hydrogenolysis of **45** using Zn−Cu couple and AcOH afforded the *Z*-iodoalkene **46** (88%), which was then subjected to the modified Stille coupling with **41**, leading to the fully protected gambierol **47** as a single stereoisomer in quantitative yield. The remaining sequence was that of deprotection. Although removal of the Piv group with DIBALH proceeded cleanly, all attempts to remove the silyl groups under various conditions including the use of TBAF, HF·py, TASF, and $SiF_4$ were unsuccessful. The triene moiety seemed to be unstable under the desilylation conditions employed.

The same problem was reported by Sasaki and was solved by deprotection before synthesizing the triene side chain.[5] Thus, removal of the Piv group of **46** with DIBALH afforded **49** in quantitative yield (Scheme 10). Deprotection of the bis-silyl ether **49** with $SiF_4$ proceeded smoothly, leading to the corresponding triol **50**.[25] Finally, the iodoalkene **50** was subjected to the modified Stille coupling with **41** to give gambierol (**1**) in 72% yield. The synthetic gambierol exhibited physical and spectroscopic data identical with those reported previously (see Supporting Information).[3,5]

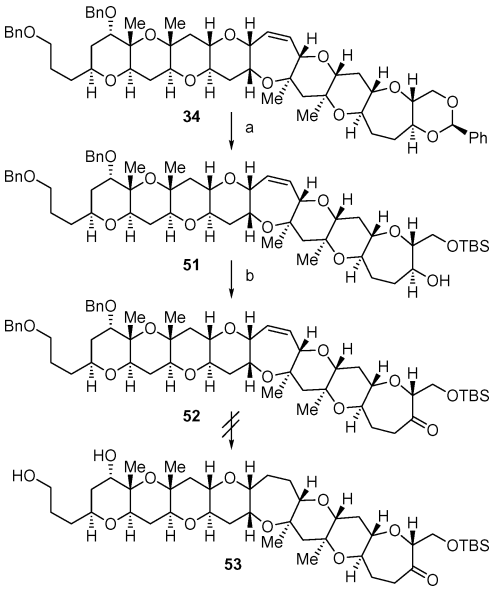
**Total Synthesis of 16-*epi*-Gambierol.** We next examined the synthesis of 16-*epi*-gambierol (**2**) starting from the octacycle **34** obtained. It was thought that since most of the polycyclic ethers isolated from nature have trans-fused systems, biological investigation of **2**, having a cis-fused DE ring system, would provide valuable information regarding the structure−activity relationship of the polyether ladder marine toxins.[26] Thus, hydrolysis of the benzylidene acetal of **34**, selective TBS

***Scheme 10.*** Completion of the Total Synthesis of Gambierol (**1**)[a]




[a] (a) DIBALH, $CH_2Cl$, −78 °C, 100% form **45** (2 steps); (b) $SiF_4$, $CH_2Cl_2$-$CH_3CN$, 0 °C; (c) **41**, $Pd_2(dba)_3$·$CHCl_3$, P(furyl)$_3$, CuI, DMSO, 40 °C, 72% (2 steps).

***Scheme 11*** [a]



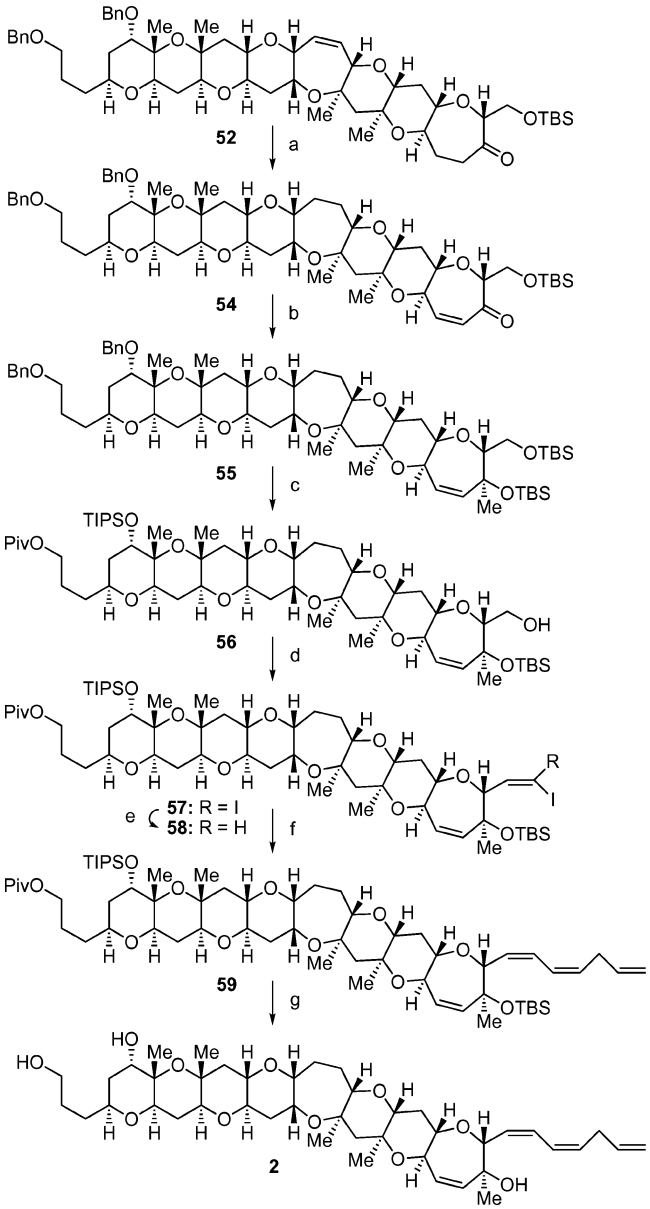

[a] (a) (i) CSA, $CH_2Cl_2$−MeOH, 35 °C; (ii) TBSCl, imidazole, $CH_2Cl_2$, 0 °C, 96% (2 steps); (b) TPAP, NMO, MS4A, $CH_2Cl_2$, rt, 95%.

protection of the primary alcohol, and oxidation of the remaining secondary hydroxy group afforded the ketone **52** (Scheme 11). Surprisingly, debenzylation of **52** with $H_2$/Pd(OH)$_2$−C resulted in the formation of a complex mixture of the products. The allylic ether moiety of the E ring seemed to be cleaved under the hydrogenation conditions.

An alternative approach is illustrated in Scheme 12. Selective hydrogenation of the double bond of **52** with $H_2$/Pd−C in the presence of $Et_3N$ as a poison,[27] conversion of the resulting ketone to the corresponding enol silyl ether, and dehydrosilylation with Pd(OAc)$_2$ gave the enone **54** in 89% yield. Grignard reaction followed by TBS protection gave the bis-silyl ether **55**

(24) Gaviña, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Marco, J. A. *J. Chem. Res.* **1986**, 330−331.
(25) Corey, E. J.; Yi, K. Y. *Tetrahedron Lett.* **1992**, *33*, 2289−2290.
(26) Very recently, Sasaki reported the biological evaluation of synthetic gambierol analogues varied with the H ring functionalities, see: Fuwa, H.; Kainuma, N.; Satake, M.; Sasaki, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2519−2522.
(27) For a example of the use of amines as a catalyst poison, see: Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076−4078.

***Scheme 12*** [a]

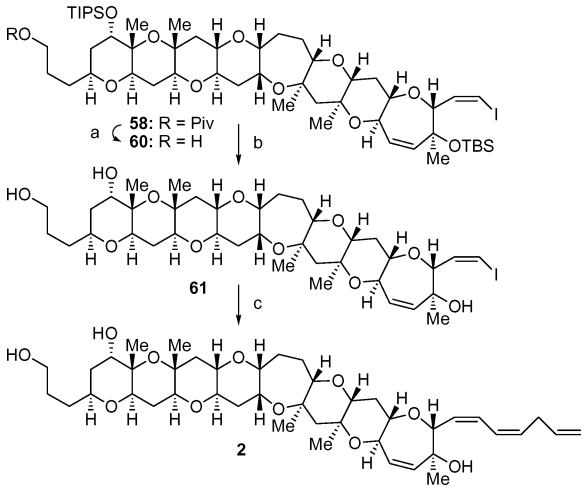



[a] (a) (i) $H_2$, Pd−C, $Et_3N$, EtOAc, rt; (ii) LiHMDS, TMSCl, $Et_3N$, THF, −78 °C; (iii) $Pd(OAc)_2$, $CH_3CN$, rt, 89% (3 steps); (b) (i) MeMgI, toluene, −78 °C; (ii) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, rt, 92% (2 steps); (c) (i) LiDBB, THF, −78 to −40 °C; (ii) PivCl, DMAP, $CH_2Cl_2$, rt; (iii) TIPSOTf, 2,6-lutidine, DMF, 60 °C; (iv) CSA, $CH_2Cl_2$−MeOH, 0 °C, 75% (4 steps); (d) (i) PCC, MS4A, $CH_2Cl_2$, rt; (ii) $Cl_4$, $PPh_3$, $CH_2Cl_2$, 0 °C, 83% (2 steps); (e) Zn−Cu, AcOH, THF−MeOH, 0 °C; (f) **41**, $Pd_2(dba)_3$·$CHCl_3$, $P(furyl)_3$, CuI, DMSO, 40 °C; (g) (i) DIBALH, $CH_2Cl_2$, −78 °C; (ii) TBAF, THF, 50 °C, 30% (4 steps).

in 92% yield. The stereochemistry of the methyl group introduced was confirmed at later stage. The benzyl groups of **55** were removed by LiDBB to give the corresponding diol,[28] which was converted to the alcohol **56** in 75% yield by Piv and TIPS protection followed by selective cleavage of the primary TBS ether. The triene side chain was constructed by PCC oxidation of **56**, diiodoolefination of the resulting aldehyde, stereoselective hydrogenolysis of the diiodoalkene **57**, and the modified Stille coupling of the resulting iodoalkene **58** with **41**. This sequential process gave the fully protected 16-*epi*-gambierol **59** in 83% yield. Removal of the Piv group with DIBALH followed by desilylation with TBAF gave 16-*epi*-gambierol (**2**) in 30% yield. In contrast to the case of **1**, the desilylation using TBAF did not decompose completely the product **2** although the yield was not satisfactory. It is interesting that the stereochemistry at C16 position exerts strong influence upon the stability of the triene moiety, and thereby the stability of the compounds themselves, located at the end of the molecule.

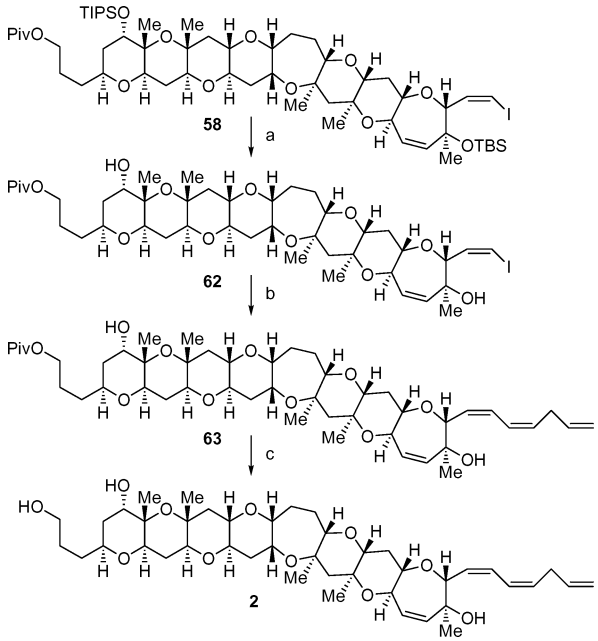
(28) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854−860.

***Scheme 13*** [a]




[a] (a) DIBALH, $CH_2Cl_2$, −78 °C, 95% from **57** (2 steps); (b) $SiF_4$, $CH_2Cl_2$−$CH_3CN$, 0 °C; (c) **41**, $Pd_2(dba)_3$·$CHCl_3$, $P(furyl)_3$, CuI, DMSO, 40 °C, ca. 60% (2 steps).

***Scheme 14*** [a]




[a] (a) $SiF_4$, $CH_2Cl_2$−$CH_3CN$, 0 °C; (b) **41**, $Pd_2(dba)_3$·$CHCl_3$, $P(furyl)_3$, CuI, DMSO, 40 °C; (c) DIBALH, $CH_2Cl_2$, −78 °C, 64% from **57** (4 steps).

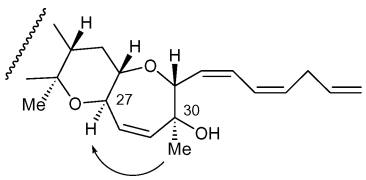



***Figure 3.*** NOE experiment on **2**.

***Figure 4.*** Energy-minimized structures (Macromodel 6.5, MM2* force field) of gambierol (upper) and 16-*epi*-gambierol (lower).

To solve this problem, we examined the deprotection of the iodoalkene **58** (Scheme 13). Treatment of **58** with DIBALH, followed by desilylation of the resulting **60** with $SiF_4$, gave the triol **61**, which was subjected to the modified Stille coupling to afford **2** smoothly. However, purification of **2** was problematic. Due to the high polarity of **2**,[29] isolation of the product from the reaction mixture was very difficult.

Scheme 14 shows the final and successful approach to the total synthesis of **2**. Desilylation of **58** with $SiF_4$ gave the diol **62**, which was coupled with **41** leading to the monoprotected stereoisomeric gambierol **63**. Finally, the Piv ester **63** was treated with DIBALH to furnish pure 16-*epi*-gambierol (**2**) in 64% yield. The stereochemistry of the methyl group on the H ring was confirmed by the NOE experiment at this stage as shown in Figure 3.

**Biological Studies.** The mouse lethality of synthetic gambierol (150 $\mu$g/kg) was equal to that of the natural product. In contrast, 16-*epi*-gambierol exhibited no toxicity at the concentration of 14 mg/kg which is 300 times as much as the $LD_{50}$ value reported for natural gambierol. As shown in Figure 4, gambierol has a flat "ladder-shaped" skeleton as do the other natural polycyclic ethers. On the other hand, 16-*epi*-gambierol is bent into a "stepladder-like" structure. These results indicate that the trans-fused polycyclic ether framework is essential to the toxicity. Probably, the bend of the molecule would inhibit the ligand−receptor interaction although the detail is not clear yet.[30]

(29) TLC analyses of **1** ($R_f$ = 0.22, $CH_2Cl_2$/MeOH = 20:1) and **2** ($R_f$ = 0.12, $CH_2Cl_2$/MeOH = 20:1) indicated the significant difference of their polarity. See Supporting Information.

(30) Recently, inhibition of brevetoxin binding to the voltage-gated sodium channel by natural gambierol was reported, see: Inoue, M.; Hirama, M.; Satake, M.; Suguyama, K.; Yasumoto, T. *Toxicon* **2003**, *41*, 469−474.

## Conclusions

Efficient total syntheses of gambierol and 16-*epi*-gambierol have been executed on the basis of a convergent strategy. Demonstrated in this study is the power of the methodology, involving the intramolecular allylation of α-chloroacetoxy ether and subsequent ring-closing metathesis, as a practical tool for constructing polycyclic ether frameworks. The longest linear sequence leading to **1** is 66 steps with 1.2% overall yield, and the total number of the steps is 102. The synthesis and biological investigation of **2** demonstrates clearly the importance of the trans-fused framework for the toxicity of polycyclic ethers. The novel method for the synthesis of *Z*-iodoalkenes is also deserving of attention (see Scheme 8). Application of the present strategy to the synthesis of other marine polycyclic ethers is in progress.

**Acknowledgment.** We thank Professor T. Yasumoto (Tohoku University) for providing the $^1$H NMR spectrum of **1**, Professor M. Hirama (Tohoku University) for supporting the measurement of MALDI TOF mass spectra, Professor T. Oishi (Osaka University) and Professor M. Inoue (Tohoku University) for valuable dicussion on the intramolecular allylation of α-acetoxy ethers. This work was financially supported by the Naito Foundation and the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds; copies of $^1$H NMR spectra for selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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