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# Total Synthesis of (−)-Gambierol

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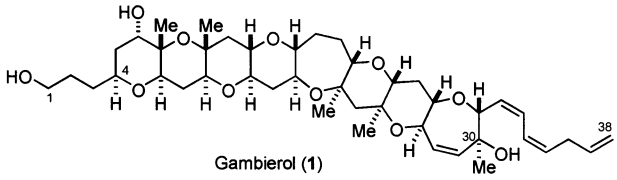
***Abstract:*** The first total synthesis of (−)-gambierol (**1**), a marine polycyclic ether toxin, has been achieved. Key features of the successful synthesis include (1) a convergent union of the ABC and EFGH ring fragments (**5** and **6**, respectively) via our developed *B*-alkyl Suzuki−Miyaura cross-coupling strategy leading to the octacyclic polyether core **4** and (2) a late-stage introduction of the sensitive triene side chain by use of $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille coupling. The ABC ring fragment **5** was synthesized in a linear manner (B → AB → ABC), wherein the A ring was formed by intramolecular hetero-Michael reaction and the C ring was constructed via 6-endo cyclization of hydroxy epoxide **7**. An improved synthetic entry to the EFGH ring fragment **6** is also described, in which $SmI_2$-induced reductive cyclization methodology was applied to the stereoselective construction of the F and H rings, leading to **6** with remarkable overall efficiency. Stereoselective hydroboration of **5** and subsequent Suzuki−Miyaura coupling with **6** provided endocyclic enol ether **45** in high yield, which was then converted to octacyclic polyether core **4**. Careful choice of the global deprotection stage was a key element for the successful total synthesis. Functionalization of the H ring and global desilylation gave (*Z*)-vinyl bromide **2**. Finally, cross-coupling of **2** with (*Z*)-vinyl stannane **3** under Corey's $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille conditions completed the total synthesis of (−)-gambierol (**1**).

## Introduction

The fused polycyclic ether class of marine natural products, exemplified by brevetoxins, ciguatoxins, and maitotoxin, has attracted a great deal of attention among chemists due to their complex molecular architecture as well as potent and diverse biological acitivities.[1,2] In 1993, Yasumoto and co-workers reported the isolation of gambierol (**1**) as a toxic constituent from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*. The gross structure and relative stereochemistry have been established by extensive NMR studies,[3] and the absolute configuration was subsequently determined by an application of a chiral anisotropic reagent.[4] The structure consists of a trans-fused octacyclic polyether core containing 18 stereogenic centers and a partially skipped triene side chain including a conjugated (*Z,Z*)-diene system (Figure 1). Gambierol exhibits potent toxicity against mice at 50 $\mu$g/kg (ip), and its symptoms caused in mice resemble those shown for ciguatoxins,[5] the principal toxin which is a very widespread seafood poisoning. This finding implies that gambierol is also responsible for ciguatera fish poisoning. However, the extremely limited availability of this toxin from natural sources has hampered detailed biological studies, including the precise biochemical mode of action. Therefore, supply of useful quantities of this natural product by practical chemical synthesis is strongly demanded, and a number of substantial efforts toward the total synthesis of gambierol have been reported to date.[6,7] Herein we describe a full account of the first total synthesis of gambierol,[8] featuring our *B*-alkyl Suzuki−Miyaura coupling strategy for the convergent synthesis of polycyclic ethers.[9,10] The synthesis




Gambierol (**1**)

***Figure 1.*** Structure of gambierol (**1**).

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(1) For reviews on marine polycyclic ether toxins, see (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3. (c) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293. (d) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228.
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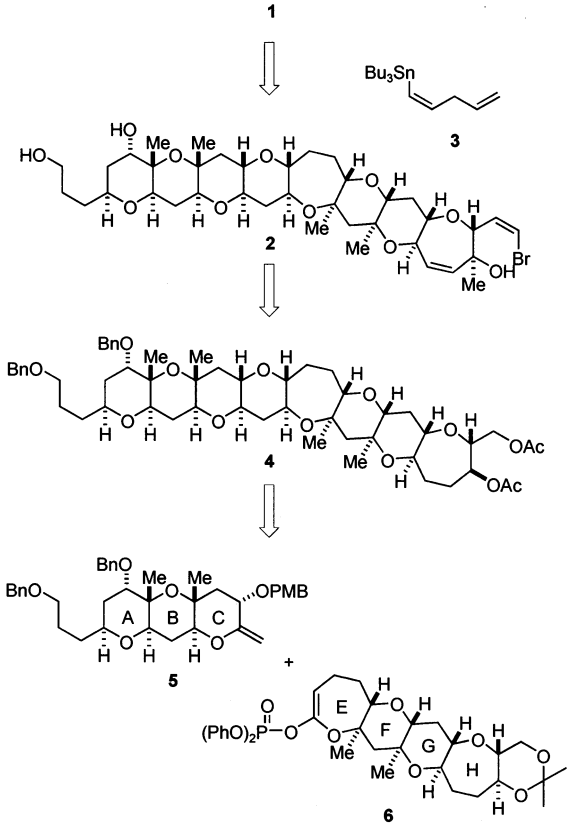
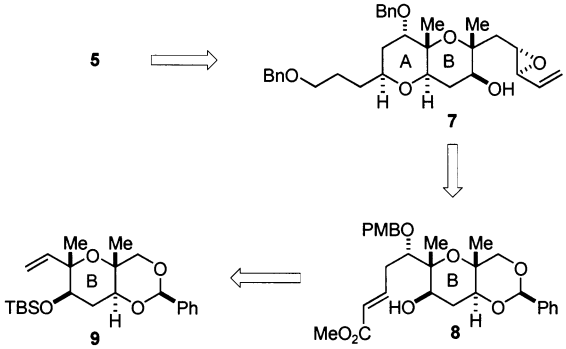
(4) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *40*, 97.
(5) (a) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929. (b) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380. (c) Murata, M.; Legrand, A.-M.; Scheuer, P. J.; Yasumoto, T. *Tetrahedron Lett.* **1992**, *33*, 525. (d) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11325. (d) Yasumoto, T.; Igarashi, T.; Legrand, A.-M.; Cruchet, P.; Chinain, M.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **2000**, *122*, 4988 and references therein.

***Scheme 1.*** Synthesis Plan of Gambierol (**1**)



***Scheme 2.*** Synthesis Plan of the ABC Ring System of Gambierol



Scheme 1. We planned to construct the triene side chain at a late stage of the synthesis due to its expected labile nature. A Stille coupling protocol[11] for the C33−C34 bond formation between (*Z*)-vinyl bromide **2** and the known (*Z*)-vinyl stannane **3**[12] reported as a model study by Kadota, Yamamoto, and co-workers[6c] was chosen as a promising candidate for the construction of the triene side chain. The vinyl bromide **2** should be available via functionalization of the H ring from the precursor octacyclic polyether core **4**. The key intermediate **4** was envisaged to be synthesized by a convergent union of the ABC ring exocyclic enol ether **5** and the EFGH ring ketene acetal phosphate **6** via the Suzuki−Miyaura coupling tactic developed in our laboratory.[10]

We planned to synthesize the ABC ring fragment **5** in a linear manner (B → AB → ABC) as shown in Scheme 2. Thus, formation of the C ring would be performed via an acid-induced 6-endo cyclization of hydroxy epoxide **7**.[13] The stereoselective construction of the A ring was envisioned to be achieved by an intramolecular hetero-Michael reaction of **8**, which should be available from the known compound **9**.[14]

Our previous approach to the EFGH ring fragment **6** relied on the *B*-alkyl Suzuki−Miyaura coupling of the F and G rings.[7b] However, the earlier synthesis lacked overall efficiency (42 steps in the longest linear sequence and 6% overall yield from the corresponding methyl ester of **14**), which prompted us to explore an alternative route for the synthesis of **6**. Recently, Nakata and co-workers have reported an iterative and efficient approach for the stereoselective construction of trans-fused six- and seven-membered ether rings based on an $SmI_2$-induced reductive cyclization.[6h,15] The most attractive feature of the Nakata protocol is that 1,3-diaxial angular methyl groups could be stereoselectively introduced. We thus envisioned a second-generation strategy, in which this $SmI_2$-induced cyclization methodology was utilized for the construction of the F and H rings (Scheme 3). As previously reported,[7b] the E ring of **6** was to be constructed as a lactone form, and construction of the F ring was envisioned to be accessible via an $SmI_2$-induced

involves as another key feature a late-stage installation of the sensitive triene side chain through $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille coupling. Our convergent and flexible strategy employed in the present total synthesis will provide easy access to structural analogues of gambierol for biological evaluation.

**Retrosynthetic Analysis.** Retrosynthetic analysis that we employed for the total synthesis of gambierol (**1**) is outlined in

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(7) (a) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019. (c) Fuwa, H.; Sasaki, M.; Tachibana, K. *Org. Lett.* **2001**, *3*, 3549.

(8) Part of this work has been communicated: see Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2981.

(9) For reviews on Suzuki−Miyaura cross-coupling reaction, see: (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 49−97. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (d) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(10) (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075. (c) Sasaki, M.; Noguchi, K.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 1425. (d) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1090. (e) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889. (f) Sasaki, M.; Tsukano, C.; Tachibana, K. *Org. Lett.* **2002**, *4*, 1747. (g) Takakura, H.; Sasaki, M.; Honda, S.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2771.

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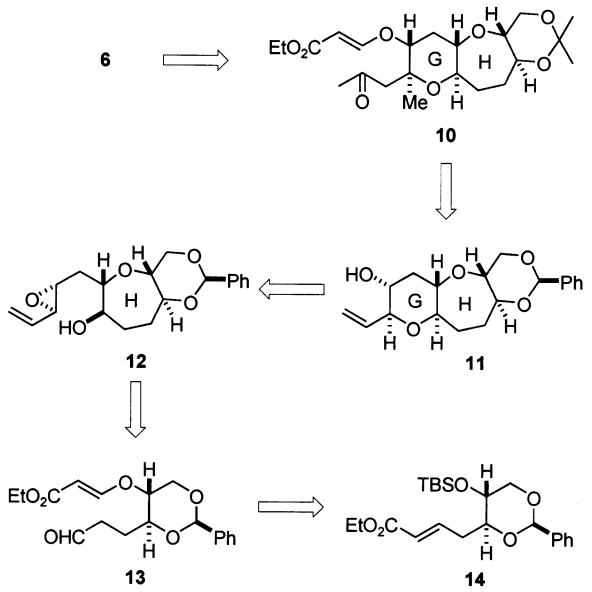
(15) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099. (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 7673.

***Scheme 3.*** Second-Generation Synthesis Plan of the EFGH Ring System of Gambierol

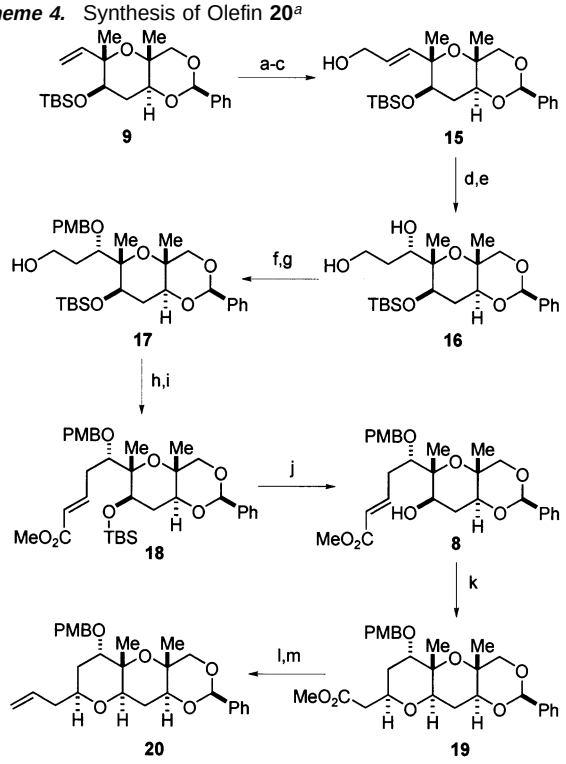


reductive cyclization of methyl ketone **10**. The G ring of the precursor **11** could be readily constructed via a 6-endo cyclization of hydroxy epoxide **12**, which was again conceived to be prepared by an $SmI_2$-induced cyclization of **13**. In turn, the aldehyde **13** should be easily derived from the known ester **14**.[16]

**Synthesis of the ABC Ring Fragment 5.** The synthesis of the ABC ring fragment **5** commenced with the known olefin **9**[14] (Scheme 4). Oxidative cleavage of the double bond [$OsO_4$, *N*-methylmorpholine *N*-oxide (NMO), and then $NaIO_4$], Horner−Wadsworth−Emmons reaction, and reduction with diisobutylaluminum hydride (DIBALH) led to allylic alcohol **15** in 87% overall yield. Sharpless asymmetric epoxidation of **15** with (−)-diethyl tartrate as a chiral auxiliary gave hydroxy epoxide, which, upon treatment with Red-Al, afforded 1,3-diol **16**[17] in good overall yield as a single stereoisomer. The differentiation of the two resultant hydroxyl groups was accomplished via anisylidene acetal formation followed by regioselective reductive cleavage with DIBALH ($CH_2Cl_2$, −40 → 0 °C), giving **17** in 80% yield for the two steps. Oxidation of alcohol **17** with $SO_3$·pyridine gave an aldehyde, which was then subjected to methyl triphenylphosphoranylidene acetate to give α,β-unsaturated ester **18** in quantitative yield over two steps. Subsequent desilylation of **18** turned out to be somewhat problematic due to the sensitive functionalities and protective groups present in **18**. After some experimentation, it was found that the desired desilylated product **8** could be obtained in high yield by treatment of **18** with tetra-*n*-butylammonium fluoride (TBAF) buffered with acetic acid.

We next executed an intramolecular hetero-Michael reaction to construct the A ring. This process could be easily accomplished by exposure of **8** to sodium hydride in THF at room temperature, giving the desired tricylic ether **19** in 86% yield as the sole product. Partial reduction of the ester moiety of **19** (1.1 equiv of DIBALH, $CH_2Cl_2$, −78 °C, 20 min) gave an aldehyde, which upon Wittig methylenation furnished olefin **20**

***Scheme 4.*** Synthesis of Olefin **20**[a]



[a] Reagents and conditions: (a) $OsO_4$, NMO, 1:1 THF/$H_2O$, rt; then $NaIO_4$, rt. (b) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, KO*t*-Bu, THF, −78 → 0 °C. (c) DIBALH, $CH_2Cl_2$, −78 °C, 87% (three steps). (d) (−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, $CH_2Cl_2$, −28 °C. (e) Red-Al, THF, −40 → 0 °C, quant (two steps). (f) *p*-$MeOC_6H_4CH(OMe)_2$, PPTS, $CH_2Cl_2$, rt. (g) DIBALH, $CH_2Cl_2$, −40 → 0 °C, 80% (two steps). (h) $SO_3$·pyridine, $Et_3N$, 1:1 DMSO/$CH_2Cl_2$, 0 °C. (i) $Ph_3P{=}CHCO_2Me$, toluene, 80 °C, quant (two steps). (j) TBAF, HOAc, THF, rt → 35 °C, 91%. (k) NaH, THF, 0 °C → rt, 86%. (l) DIBALH, $CH_2Cl_2$, −78 °C. (m) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C, 91% (two steps).

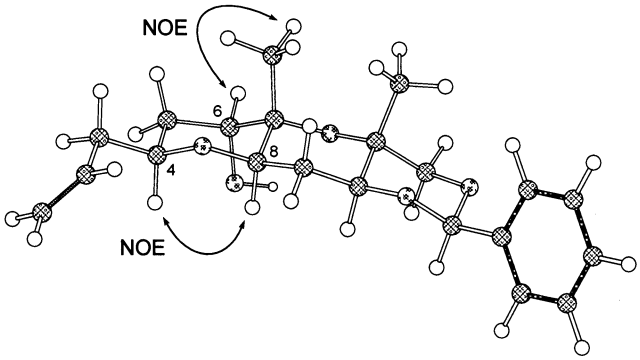


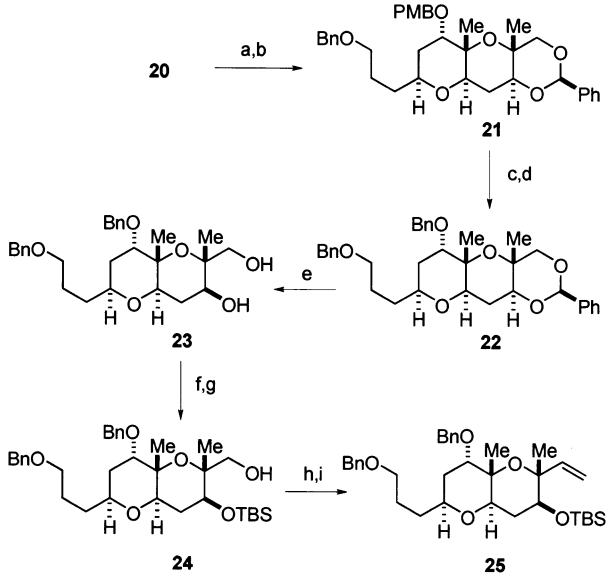

***Figure 2.*** NOE experiments on compound **20**. The PMB group is omitted for clarity.

in 91% overall yield. At this stage, the relative stereochemistry was unambiguously determined by NOE experiments as shown in Figure 2.

Hydroboration of **20** with 9-BBN followed by oxidative workup gave an alcohol, which was protected as its benzyl ether to afford **21** in 94% yield for the two steps (Scheme 5). Oxidative removal of the *p*-methoxybenzyl (PMB) group and reprotection as the benzyl ether gave bis(benzyl ether) **22** in 93% yield for the two steps. Removal of the benzylidene acetal under acidic conditions led to diol **23**. Bis-silylation followed by selective liberation of the C12[18] primary hydroxyl under acidic conditions led to alcohol **24**. Oxidation of **24** with a

(16) Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.-Q.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 618.
(17) Finan, J.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

***Scheme 5.*** Synthesis of AB Ring Fragment **25**[a]



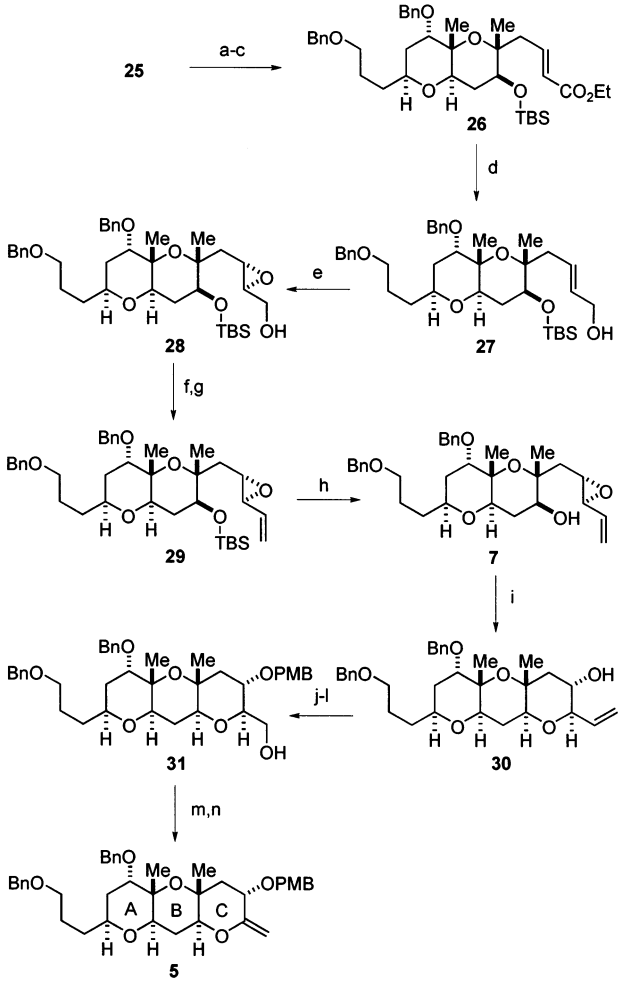

[a] Reagents and conditions: (a) 9-BBN, THF, rt; then aq $NaHCO_3$, 30% $H_2O_2$, rt. (b) BnBr, KO*t*-Bu, *n*-$Bu_4NI$, THF, rt, 94% (two steps). (c) DDQ, pH 7 phosphate buffer, $CH_2Cl_2$, rt. (d) BnBr, KO*t*-Bu, *n*-$Bu_4NI$, THF, rt, 93% (two steps). (e) *p*-TsOH, 9:1 MeOH/$CHCl_3$, rt, 95%. (f) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C. (g) CSA, MeOH, rt, 92% (two steps). (h) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, rt, 95%. (i) Tebbe reagent, THF, 0 °C, 90%.

catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) and NMO[19] gave an aldehyde, which was then treated with Tebbe reagent (THF, 0 °C)[20] to afford olefin **25** in 86% overall yield from **24**. In this reaction, conventional Wittig methylenation resulted in a poor yield of **25**.

Construction of the C ring and completing the synthesis of the ABC ring fragment **5** are summarized in Scheme 6. Hydroboration of **25** with 9-BBN followed by oxidative workup gave an alcohol, which was oxidized to the aldehyde and subsequently homologated by Horner−Wadsworth−Emmons reaction to give α,β-unsaturated ester **26** in 90% overall yield. DIBALH reduction led to allylic alcohol **27** in nearly quantitative yield. Subsequent Sharpless asymmetric epoxidation of **27** with (+)-diethyl tartrate was somewhat unsatisfactory with regard to its diastereoselectivity and gave an inseparable mixture (ca. 6:1) of diastereomers, favoring the desired α-epoxide **28**. On the other hand, oxidation with *m*-chloroperbenzoic acid ($CH_2Cl_2$, 0 °C) led exclusively to the desired **28** in almost quantitative yield.[14] Oxidation of **28** was followed by Wittig methylenation of the derived aldehyde to afford olefin **29** in 87% yield for the two steps. Removal of the TBS group with TBAF gave hydroxy epoxide **7**, which was exposed to mild acidic conditions (PPTS, $CH_2Cl_2$, room temperature) to effect 6-endo cyclization, giving tricyclic ether **30** in 96% yield for the two steps. The relative stereochemistry of **30** was unambiguously established on the basis of NOE experiments and a large coupling constant of $J_{13,14} = 9.2$ Hz (Figure 3).

Conversion of tricyclic ether **30** to the ABC ring fragment **5** was carried out in a straightforward manner. Protection of **30** as the PMB ether was followed by oxidative cleavage of the

***Scheme 6.*** Synthesis of ABC Ring Fragment **5**[a]




[a] Reagents and conditions: (a) 9-BBN, THF, rt; then aq $NaHCO_3$, 30% $H_2O_2$, rt. (b) $SO_3$·pyridine, $Et_3N$, 1:1 DMSO/$CH_2Cl_2$, 0 °C. (c) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, KO*t*-Bu, THF, −78 → 0 °C, 90% (three steps). (d) DIBALH, $CH_2Cl_2$, −78 °C, 98%. (e) *m*CPBA, $CH_2Cl_2$, 0 °C, 99%. (f) $SO_3$·pyridine, $Et_3N$, 1:1 DMSO/$CH_2Cl_2$, 0 °C. (g) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C, 87% (two steps). (h) TBAF, THF, rt, 98%. (i) PPTS, $CH_2Cl_2$, rt, 98%. (j) PMBCl, KO*t*-Bu, *n*-$Bu_4NI$, THF, rt. (k) $OsO_4$, NMO, 1:1 THF/$H_2O$, rt; then $NaIO_4$, rt. (l) $NaBH_4$, MeOH, 0 °C → rt, 86% (three steps). (m) $I_2$, $PPh_3$, imidazole, benzene, rt, 95%. (n) KO*t*-Bu, THF, 0 °C, 91%.

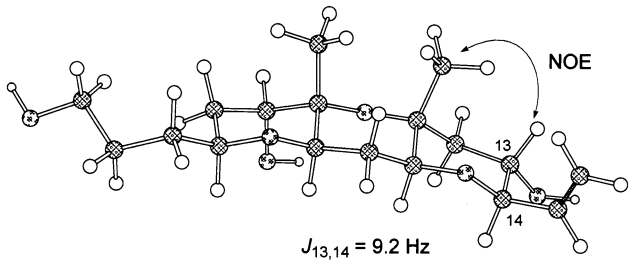
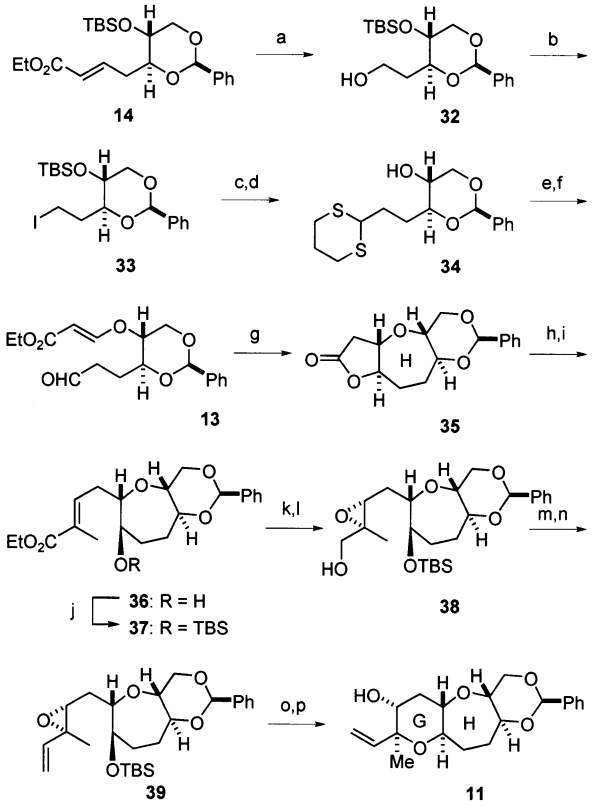



***Figure 3.*** Determination of stereochemistry of compound **30**. Benzyl groups are omitted for clarity.

double bond ($OsO_4$, NMO, and then $NaIO_4$), and subsequent reduction of the derived aldehyde led to alcohol **31** in good overall yield. Iodination of the primary alcohol under standard conditions followed by base treatment (KO*t*-Bu, THF, 0 °C) afforded the ABC ring exocyclic enol ether **5** in 86% yield for the two steps. The overall sequence proceeded in 36 steps from **9** and in 18% overall yield, and thus the ABC ring fragment **5** could be synthesized in multigram quantities.

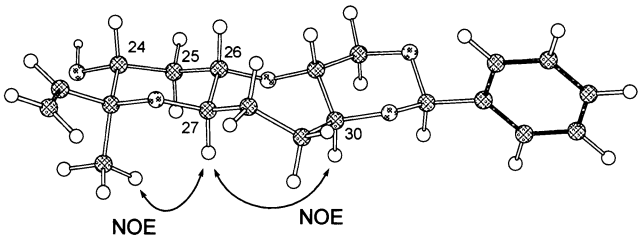
(18) The numbering of carbon atoms of all compounds in this paper corresponds to that of gambierol.
(19) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(20) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

***Scheme 7.*** Synthesis of GH Ring Fragment **11**[a]




[a] Reagents and conditions: (a) $O_3$, 1:1 MeOH/$CH_2Cl_2$, −78 °C; then $NaBH_4$, 0 °C, 96%. (b) $I_2$, $PPh_3$, imidazole, THF, rt, 99%. (c) 1,3-Dithiane, *n*-BuLi, THF, −20 °C; then **33**, 0 °C. (d) TBAF, THF, rt, 95% (two steps). (e) Ethyl propiolate, NMM, $CH_2Cl_2$, rt. (f) MeI, $NaHCO_3$, aq $CH_3CN$, rt, 94% (two steps). (g) $SmI_2$, MeOH, THF, rt, 70%. (h) DIBALH, $CH_2Cl_2$, −78 °C; (i) $Ph_3P{=}C(Me)CO_2Et$, toluene, 80 °C, 97% (two steps). (j) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, quant. (k) DIBALH, $CH_2Cl_2$, −78 °C. (l) (−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, $CH_2Cl_2$, −20 °C, 97% (two steps). (m) $SO_3$·pyridine, $Et_3N$, 1:1 DMSO/$CH_2Cl_2$, 0 °C. (n) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C, 94% (two steps). (o) TBAF, THF, rt. (p) PPTS, $CH_2Cl_2$, rt, 88% (two steps).

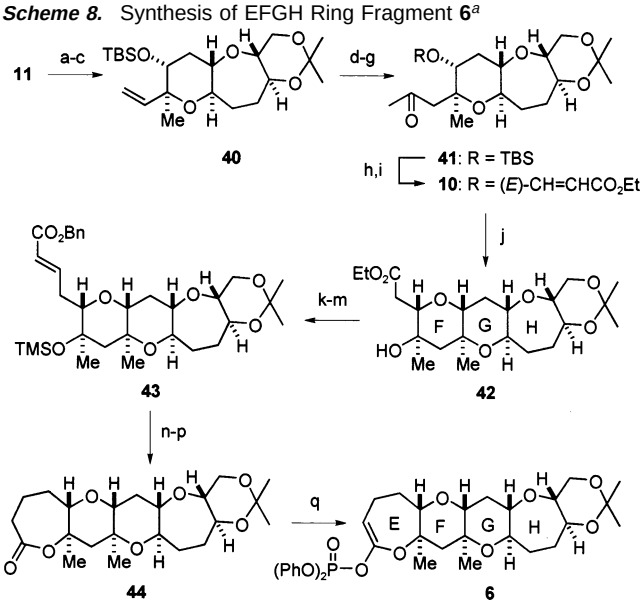
**Second-Generation Synthesis of EFGH Ring Fragment 6.** An improved second-generation synthesis of the EFGH ring fragment **6** started with the known ester **14**[16] (Scheme 7). Ozonolysis followed by reductive workup with $NaBH_4$ afforded alcohol **32**, which was then iodinated under the standard conditions to give **33** in 99% yield. Treatment of iodide **33** with lithiated dithiane (1,3-dithiane, *n*-BuLi, THF, −20 °C) and subsequent removal of the silyl protective group gave alcohol **34** in 95% yield for the two steps. The $\beta$-alkoxyacrylate moiety was next incorporated by treatment with ethyl propiolate and *N*-methylmorpholine (NMM), and subsequently the dithioacetal moiety was removed to give aldehyde **13** (91% yield for the two steps). As expected, reductive cyclization of **13** with $SmI_2$ in the presence of methanol (THF, room temperature) proceeded stereoselectively and the desired $\gamma$-lactone **35** was obtained in 70% yield along with a minute amount of the hydroxy ester (3% yield, not shown).[15] Lactone **35** was then converted to $\alpha,\beta$-unsaturated ester **36** in high overall yield by DIBALH reduction and Wittig reaction of the derived lactol. Protection of the secondary hydroxyl within **36** as the TBS ether gave **37** quantitatively. DIBALH reduction of the ester moiety gave allylic alcohol, which was subjected to Sharpless asymmetric epoxidation with (−)-diethyl tartrate as a chiral auxiliary to afford hydroxy epoxide **38** in high overall yield as a single stereoisomer. Oxidation with $SO_3$·pyridine followed by Wittig methylenation of the derived aldehyde afforded vinyl epoxide **39** in 94% yield for the two steps. After desilylation, 6-endo cylization of the resultant alcohol **12** was performed by exposure to PPTS in $CH_2Cl_2$ at room temperature to give the GH ring system **11** in 88% yield for the two steps. The relative stereochemistry of **11** was determined on the basis of $^1H$ NMR coupling constants and NOE experiments (Figure 4).




$J_{24,25\alpha}$ = 11.9 Hz, $J_{25\alpha,26}$ = 11.3 Hz, $J_{26,27}$ = 9.5 Hz

***Figure 4.*** Structure determination of compound **11**.

***Scheme 8.*** Synthesis of EFGH Ring Fragment **6**[a]




[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C. (b) EtSH, $Zn(OTf)_2$, $NaHCO_3$, $CH_2Cl_2$, rt, 85% (two steps). (c) $Me_2C(OMe)_2$, PPTS, $CH_2Cl_2$, rt, 92%. (d) 9-BBN, THF, rt; then aq $NaHCO_3$, 30% $H_2O_2$, rt. (e) $SO_3$·pyridine, $Et_3N$, 1:1 DMSO/$CH_2Cl_2$, 0 °C. (f) MeMgBr, toluene, −78 °C. (g) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, rt, 86% (four steps). (h) TBAF, THF, rt. (i) Ethyl propiolate, NMM, $CH_2Cl_2$, rt, 99% (two steps). (j) $SmI_2$, MeOH, THF, 0 °C, 87%. (k) TMSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 96%. (l) DIBALH, $CH_2Cl_2$, −78 °C. (m) $Ph_3P{=}CHCO_2Bn$, toluene, rt, 95% (two steps). (n) TBAF, HOAc, THF, rt, 93%. (o) $H_2$, Pd/C, 2:1 MeOH/THF, rt. (p) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, 1:1 THF/toluene, rt; then DMAP, toluene, 110 °C, 99% (two steps). (q) KHMDS (3 equiv), $(PhO)_2P(O)Cl$ (10 equiv), 10:1 THF/HMPA (10 mM), −78 °C, quant.

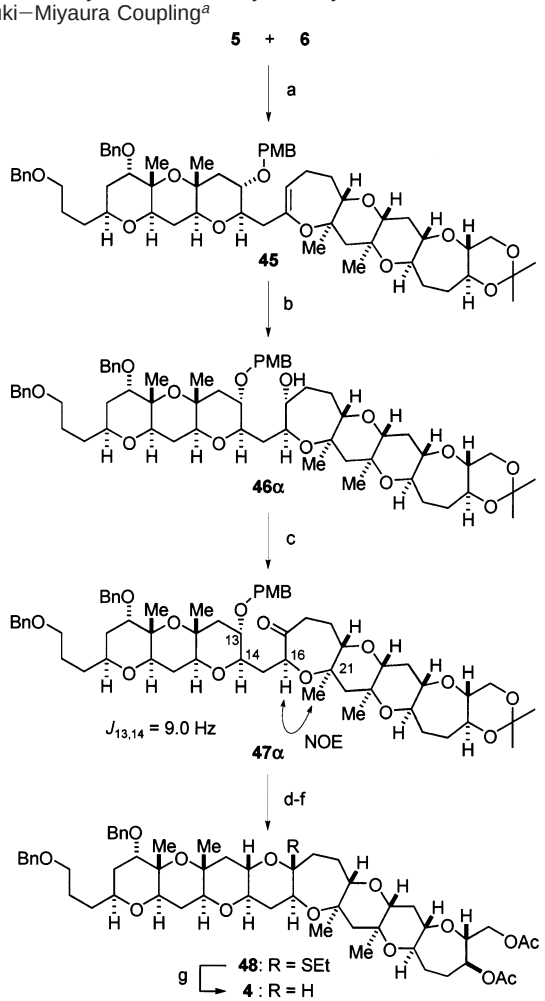
Protection of the secondary hydroxyl within **11** as its TBS ether followed by replacement of the benzylidene acetal with the acetonide group led to **40** in 78% overall yield (Scheme 8). Olefin **40** was then converted to methyl ketone **41** by a routine four-step sequence of reactions. Thus, hydroboration of **40** with 9-BBN followed by oxidative workup gave primary alcohol, which was oxidized with $SO_3$·pyridine to the aldehyde. Treatment with MeMgBr (toluene, −78 °C) and further oxidation of the derived secondary hydroxyl with TPAP/NMO afforded methyl ketone **41** (86% overall yield from **40**). Desilylation followed by treatment with ethyl propiolate and NMM afforded

$\beta$-alkoxy acrylate **10** in nearly quantitative yield for the two steps. Exposure of **10** to $SmI_2$ (methanol, THF, 0 °C) again effected stereoselective ring closure of the F ring furnished with 1,3-diaxial angular methyl groups to give the FGH ring system **42** in 87% yield as a single stereoisomer. Protection of the tertiary hydroxyl as the TMS ether (TMSOTf, 2,6-lutidine), followed by half-reduction of the ester moiety and Wittig reaction with benzyl triphenylphosporanylidene acetate, afforded $\alpha,\beta$-unsaturated benzyl ester **43** in excellent overall yield (93%). Desilylation by TBAF buffered with acetic acid was followed by concomitant removal of the benzyl group and saturation of the double bond to provide hydroxy acid, which was then subjected to Yamaguchi lactonization.[21] These sequences provided lactone **44** in 93% overall yield. Spectroscopic data ($^1$H and $^{13}$C NMR, $[\alpha]_D$, IR, and HRMS) of **44** thus prepared were exactly matched with those of the previously reported product.[7b] Finally, conversion of **44** into the EFGH ring ketene acetal phosphate **6** was accomplished by using the modified Nicolaou protocol [3 equiv of KHMDS, 10 equiv of $(PhO)_2P(O)Cl$, 10:1 THF/HMPA (10 mM), −78 °C, quant].[22] Thus, we completed an improved synthesis of the EFGH ring fragment **6** in 33 steps and 22% overall yield from the known compound **14**. This remarkably efficient synthesis allowed preparation of **6** in multigram quantities.

**Convergent Union of the Two Key Intermediates: Synthesis of the Octacyclic Polyether Core.** With the requisite key intermediates **5** and **6** in hand, we next turned our attention to the crucial coupling of these components via the *B*-alkyl Suzuki−Miyaura coupling strategy (Scheme 9). Hydroboration of the ABC ring exocyclic enol ether **5** with 9-BBN in THF at room temperature produced the corresponding alkylborane, which was in situ reacted with the EFGH ring ketene acetal phosphate **6** (1.4 equiv) in the presence of aqueous $Cs_2CO_3$ (3 equiv) and $PdCl_2$(dppf) (50 mol %) in DMF at 50 °C for 22 h. The desired cross-coupled product **45** was obtained in gratifying 86% yield. This remarkable yield represents the power and feasibility of our *B*-alkyl Suzuki−Miyaura coupling chemistry.

Treatment of **45** with $BH_3$·THF (THF, room temperature, 1 h) followed by oxidative workup led to the desired alcohol **46α** in 87% yield as the sole product. Oxidation of **46α** with TPAP/NMO gave rise to ketone **47α** in 98% yield. At this stage, the relative stereochemistry of ketone **47α** was unambiguously established by NMR analyses. The large coupling constant of $J_{13,14}$ = 9.0 Hz confirmed the trans relationship of H13 and H14 protons, whereas the syn relationship of H16 and C21 methyl group was established by NOESY experiments. In contrast, exposure of **45** with $BH_3$·$SMe_2$ (THF, room temperature, 3 h) followed by oxidative workup gave a mixture of diastereomers **46α** and **46*β*** (71% and 11% yields, respectively), which were readily separable by flash chromatography (Scheme 10). Oxidation of diastereomer **46*β*** with TPAP/NMO gave epimeric ketone **47*β*** in 90% yield,[23] which upon treatment with DBU (toluene, 110 °C, 1 day) gave a 3:2 mixture of **47α** and **47*β***, favoring the thermodynamically more stable isomer **47α**. From these results, we reached an intriguing conclusion that hydroboration of endocyclic enol ether **45** occurred from the sterically more hindered α-face of the molecule to afford **46α**.

***Scheme 9.*** Synthesis of Octacyclic Polyether Core **4** via *B*-alkyl Suzuki−Miyaura Coupling[a]




[a] Reagents and conditions: (a) 9-BBN, THF, rt; then **6**, aq $Cs_2CO_3$, $PdCl_2$(dppf)·$CH_2Cl_2$, DMF, 50 °C, 86%. (b) $BH_3$·THF, THF, rt; then aq NaOH, 30% $H_2O_2$, rt, 87%. (c) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, rt, 98%. (d) DDQ, pH 7 phosphate buffer, $CH_2Cl_2$, rt. (e) EtSH, $Zn(OTf)_2$, $CH_2Cl_2$, rt. (f) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 75% (three steps). (g) $Ph_3SnH$, AIBN, toluene, 110 °C, 95%.

Oxidative removal of the PMB protective group within **47α** gave the corresponding hemiketal, which was then exposed to ethanethiol in the presence of zinc trifluoromethanesulfonate to effect mixed-thioketal formation with concomitant loss of the acetonide group (Scheme 9). The liberated hydroxyl groups were then acylated to afford diacetate **48** in 75% yield over the three steps. Finally, desulfurization under radical reduction conditions ($Ph_3SnH$, AIBN, toluene, 110 °C)[24] proceeded cleanly to furnish the octacyclic polyether core **4** in 95% yield.

**Model Studies for the Construction of Triene Side Chain.** Having succeeded in obtaining the key intermediate **4**, all that is necessary to complete the total synthesis of **1** is functionalization of the H ring and stereoselective installation of the sensitive triene side chain. Especially, stereoselective construction of a partially skipped triene side chain that includes a

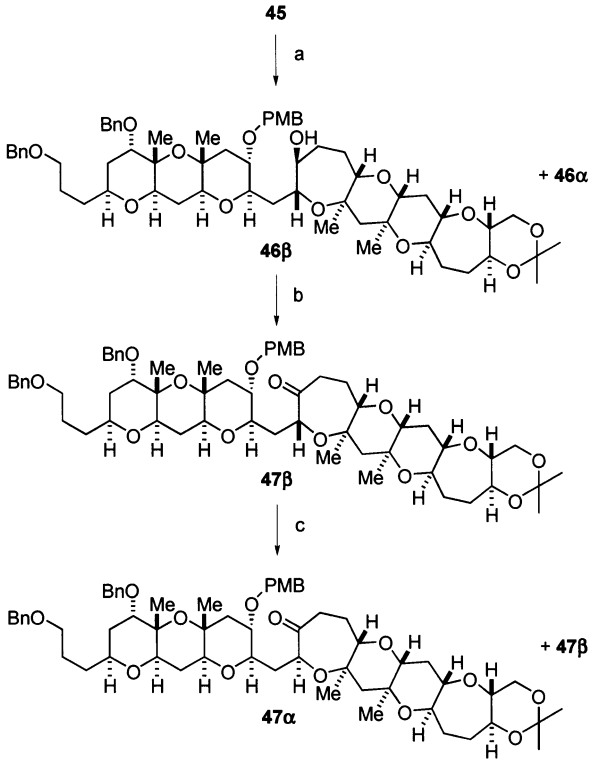
(21) (a) Yamaguchi, M.; Inanaga, J.; Hirata, K.; Sasaki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Mulzer, J.; Mareski, P. A.; Bushmann, J.; Luger, P. *Synthesis* **1992**, 215.

(22) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467.

(23) The $^1$H NMR spectrum of epimeric ketone **47*β*** was different from that of ketone **47α**, indicating that we can rule out the possibility of epimerization during the oxidation with TPAP/NMO.

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

***Scheme 10*** [a]

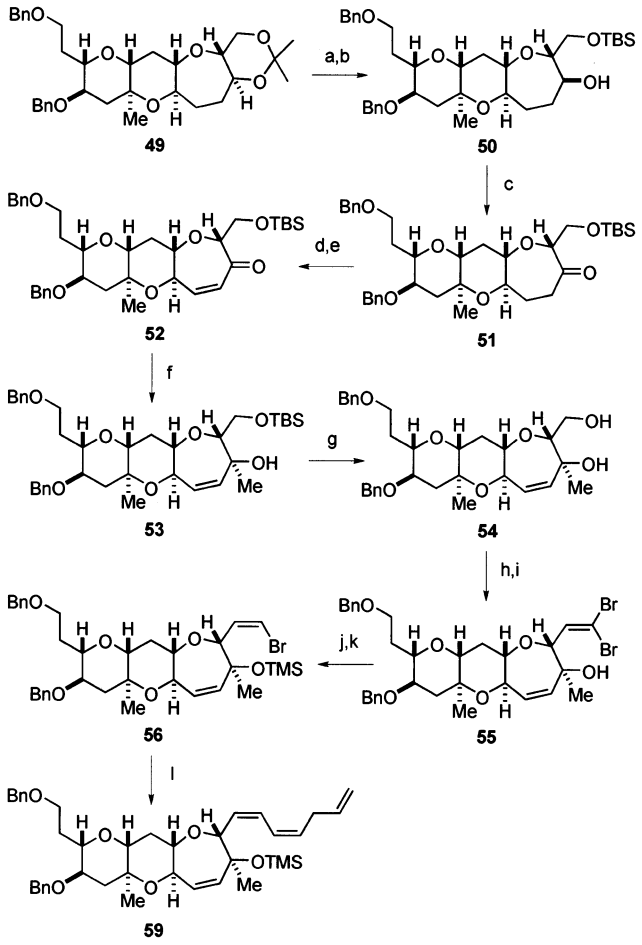



[a] Reagents and conditions: (a) $BH_3$·$SMe_2$, THF, rt; then aq NaOH, 30% $H_2O_2$, rt; **46α**, 71%; **46*β***, 11%. (b) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, rt, 90%. (c) DBU, toluene, 110 °C, quant (**47α**:**47*β*** = 3:2).

conjugated (*Z*,*Z*)-diene system represents a formidable synthetic challenge. As described in the synthetic plan, a modified Stille coupling protocol for the C33−C34 bond formation is an appropriate candidate for the construction of the triene side chain.

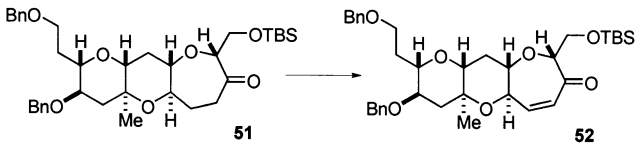
Initially, we tried to synthesize model compound **59** in order to establish a feasible route for the completion of the total synthesis (Scheme 11). Removal of the acetonide group of **49**[7b] under acidic conditions followed by selective protection of the liberated primary hydroxyl gave alcohol **50** (96% yield for the two steps), which was oxidized with TPAP/NMO to afford ketone **51** in 92% yield. Subsequent conversion of **51** into enone **52** turned out to be somewhat problematic. Conventional selenium-based methodology failed to give **52** (Table 1, entry 1). *o*-Iodoxybenzoic acid- (IBX-) mediated dehydrogenation reaction, recently reported by Nicolaou and co-workers,[25] was also ineffective in the present case (entry 2). Exposure of the kinetically formed lithium enolate of **51** to *N*-(*tert*-butyl)-phenylsulfimidoyl chloride (THF, −78 °C)[26] gave **52** in only a modest yield (entry 3). The Ito−Saegusa protocol[27] also gave a comparable result. Thus, **51** was treated with LiHMDS and the derived enolate was trapped with TMSCl and $Et_3N$ to give the corresponding enol silyl ether, which, without purification, was treated with $Pd(OAc)_2$ in acetonitrile at room temperature to afford **52** in 57% yield (entry 4). After several experiments, it was discovered that treatment of **51** with LiHMDS *in the presence of TMSCl and Et₃N* cleanly gave the corresponding enol silyl ether. Upon oxidation of the enol silyl ether with $Pd(OAc)_2$, the desired enone **52** was obtained in 92% yield (entry 5). This remarkable improvement may be ascribed to the lability of ketone **51** and/or the corresponding lithium enolate under the reaction conditions. Stereoselective introduction of the C30 methyl group was accomplished by treatment of **51**

***Scheme 11.*** Synthesis of Fully Functionalized FGH Ring System[a]




[a] Reagents and conditions: (a) CSA, MeOH, rt. (b) TBSCl, imidazole, DMF, 0 °C, 96% (two steps). (c) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, rt, 92%. (d) LiHMDS, TMSCl, $Et_3N$, THF, −78 °C. (e) $Pd(OAc)_2$, MeCN, rt, 92% (two steps). (f) MeMgBr, toluene, −78 °C, 96%. (g) TBAF, THF, rt, 87%. (h) $SO_3$·pyridine, $Et_3N$, 1:1 DMSO/$CH_2Cl_2$, 0 °C. (i) $CBr_4$, $PPh_3$, $Et_3N$, $CH_2Cl_2$, 0 °C, 84% (two steps). (j) TMSOTf, $Et_3N$, $CH_2Cl_2$, 0 °C, 93%. (k) *n*-$Bu_3SnH$, $Pd(PPh_3)_4$, benzene, rt, 81%. (l) **3**, $Pd(PPh_3)_4$, CuCl, LiCl, 1:1 DMSO/THF, 60 °C, 95%.

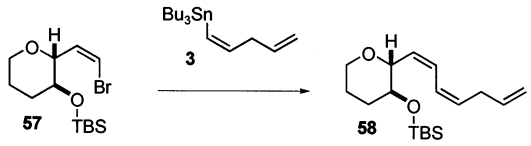
***Table 1.*** Conversion of Ketone **51** to Enone **52**




| entry | reagents and conditions | % yield |
|---|---|---|
| 1 | (a) LiHMDS, THF, −78 °C; then PhSeBr, −78 °C → rt; (b) 30% $H_2O_2$, THF, rt | 0 |
| 2 | IBX, 1:1 DMSO/toluene, 55 °C | 0 |
| 3 | LiHMDS, THF, −78 °C; then PhS(Cl)=N*t*-Bu, −78 °C | 61 |
| 4 | (a) LiHMDS, THF, −78 °C; then TMSCl, $Et_3N$, −78 °C; (b) $Pd(OAc)_2$, MeCN, rt | 57 |
| 5 | (a) LiHMDS, TMSCl, $Et_3N$, THF, −78 °C; (b) $Pd(OAc)_2$, MeCN, rt | 92 |

(25) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.
(26) Mukaiyama, T.; Matsuo, J.; Kitagawa, H. *Chem. Lett.* **2000**, 1250.
(27) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

***Table 2.*** Stille Coupling of (*Z*)-Vinyl Bromide **57** and (*Z*)-Vinyl Stannane **3**[a]




| entry | **3** (equiv) | catalyst | ligand[b] | cocatalyst[c] (equiv) | additive (equiv) | solvent | temp | % yield |
|---|---|---|---|---|---|---|---|---|
| 1 | 2.0 | $Pd_2(dba)_3CHCl_3$ | TFP | CuI (1.6) | | DMSO/THF (1:1) | rt | 49[e] |
| 2 | 2.0 | $Pd_2(dba)_3CHCl_3$ | TFP | CuI (1.0) | | DMSO/THF (1:1) | 60 °C | 50 |
| 3 | 1.5 | $Pd(PPh_3)_4$ | | | *i*-$Pr_2NEt$ (10) | DMF | rt | ND[d] |
| 4 | 1.5 | $PdCl_2(MeCN)_2$ | TFP | | | DMF | 60 °C | 39[e] |
| 5 | 1.5 | $Pd_2(dba)_3CHCl_3$ | $Ph_3As$ | | | DMF | 60 °C | 28[e] |
| 6 | 2.0 | $Pd_2(dba)_3CHCl_3$ | TFP | CuTC (10) | | DMSO/THF (1:1) | 60 °C | 69 |
| 7 | 2.0 | $Pd_2(dba)_3CHCl_3$ | TFP | CuTC (10) | | DMSO/THF (1:1) | rt | 75 |
| 8 | 2.0 | $Pd(PPh_3)_4$ | | CuCl (10) | LiCl (12) | DMSO/THF (1:1) | rt | 49[e] |
| 9 | 2.0 | $Pd(PPh_3)_4$ | | CuCl (10) | LiCl (12) | DMSO/THF (1:1) | 60 °C | 81 |

[a] All reactions were carried out using Pd catalyst (20 mol%) and ligand (80 mol%) for 2 days. [b] TFP = tri(2-furyl)phosphine. [c] TC = thiophene-2-carboxylate. [d] Yield not determined (18% conversion based on $^1H$ NMR analysis). [e] Vinyl bromide **57** was not consumed completely and the yield was estimated by $^1H$ NMR analysis of an inseparable mixture of **57** and **58**.

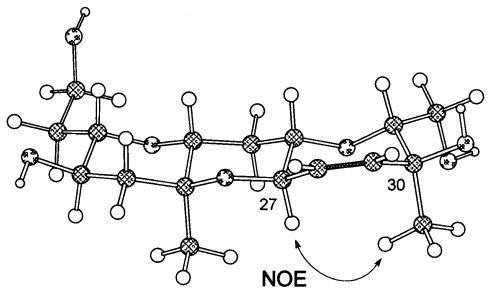



***Figure 5.*** NOE experiments on compound **53**. The benzyl and TBS groups are omitted for clarity.

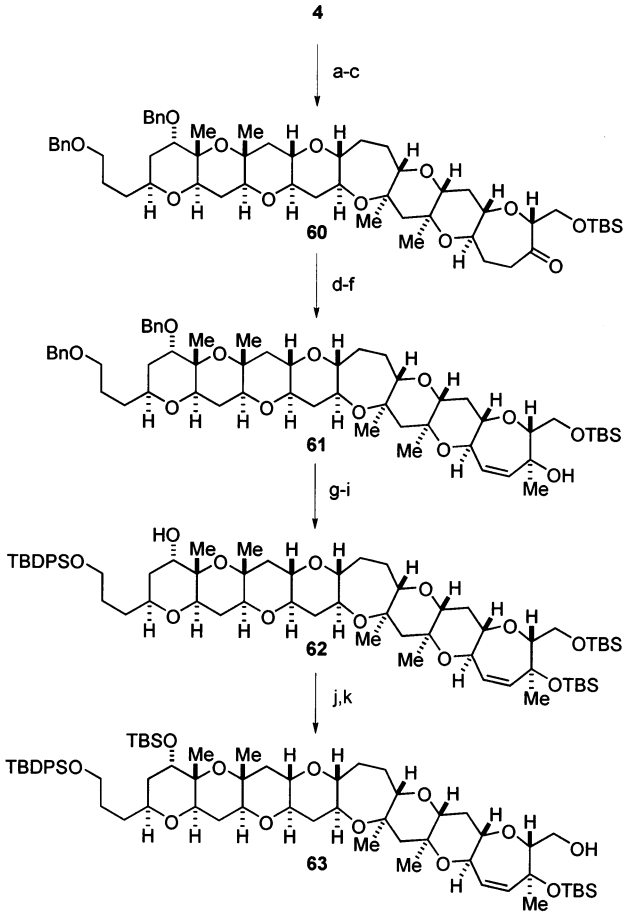
with MeMgBr in toluene at −78 °C[28] to afford tertiary alcohol **53** as a single stereoisomer. Stereochemistry at the C30 quaternary stereocenter was determined by NOE experiments as shown in Figure 5. Subsequent desilylation with TBAF gave diol **54** in 84% overall yield from **52**. Selective oxidation of the primary hydroxyl followed by Corey−Fuchs reaction ($CBr_4$, $PPh_3$, $Et_3N$)[29] of the derived aldehyde gave dibromoolefin **55** (84% yield over two steps). After protection of the tertiary alcohol as its TMS ether, stereoselective hydrogenolysis of the dibromoolefin with *n*-$Bu_3SnH$ and $Pd(PPh_3)_4$[30] afforded (*Z*)-vinyl bromide **56** in 81% yield, setting the stage for the construction of the triene side chain.

The Stille coupling of **56** with the known (*Z*)-vinyl stannane **3**[12] was quite difficult due to low reactivity of the sterically hindered (*Z*)-vinyl stannane as well as the (*Z*)-vinyl bromide. Moreover, an attempt to bring about the coupling of a simple model substrate (*Z*)-vinyl bromide **57**[31] with **3** under the modified Stille conditions [$Pd_2(dba)_3$•$CHCl_3$, (2-furyl)$_3$P, CuI, DMSO/THF[32]], which was originally reported by Liebeskind et al.[33] and successfully utilized in Yamamoto's model study,[6c] gave the cross-coupled product **58** in only a modest yield (Table 2, entries 1 and 2). Therefore, we reinvestigated the cross-coupling reaction to establish the optimal conditions. Not unexpectedly, in the absence of copper(I) salt, only poor yield and low conversion were observed (entries 3−5). Use of copper(I) thiophene-2-carboxylate (CuTC)[34] or CuCl advantageously accelerated the reaction and improved the yield of **58** (entries 6−9). Observed improvements of the Stille coupling by the addition of CuTC or CuCl could be ascribed to facile in situ generation of a more reactive organocopper species as a nucleophile that facilitates the transmetalation step in the catalytic cycle. Especially, the $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille conditions (1:1 DMSO/THF, 60 °C) developed by Corey and co-workers[35] were quite suitable for this process (entry 9). Notably, under these conditions the cross-coupling reaction proceeded with retention of olefin stereochemistry. Application of these optimal conditions to the Stille coupling of (*Z*)-vinyl bromide **56** with **3** produced the desired product **59** in 95% isolated yield (Scheme 11). Again, none of the other isomer was detected in the $^1H$ NMR spectrum of the reaction mixture.

**Completion of Total Synthesis of (−)-Gambierol.** With a reliable precedent for the stereoselective construction of the sensitive triene side chain established, we proceeded forward to complete the total synthesis with confidence. Removal of the acetyl groups within **4** followed by selective protection of the C32 primary hydroxyl and subsequent oxidation of the remaining secondary hydroxyl with TPAP/NMO then produced ketone **60** in 69% overall yield (Scheme 12). Treatment of **60** with LiHMDS in the presence of TMSCl and $Et_3N$ as described above gave the corresponding enol silyl ether, which upon immediate exposure to $Pd(OAc)_2$ in acetonitrile at room temperature afforded enone. Subsequent Grignard reaction with MeMgBr (toluene, −78 °C) furnished tertiary alcohol **61** in 94% overall yield as a single stereoisomer. After protection of the tertiary hydroxyl as its TBS ether,[36] reductive cleavage of the benzyl ethers by exposure to excess lithium di-*tert*-butylbiphenylide (LiDBB),[37] followed by protection of the C1 primary hydroxyl as the *tert*-butyldiphenylsilyl (TBDPS) ether,

(28) Feng, F.; Murai, A. *Chem. Lett.* **1992**, 1587.
(29) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(30) (a) Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* **1996**, *37*, 6759. (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716. (c) Uenishi, J.; Kawahama, R.; Yonemistu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965.
(31) The corresponding iodide was too unstable to be used.
(32) A mixed solvent system of 1:1 DMSO/THF was used in the present study due to the low solubility of (*Z*)-vinyl stannane **3** in DMSO.
(33) (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
(34) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.
(35) Han, X.; Stolz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.
(36) TMS and TES protective groups could not survive the next reductive debenzylation with LiDBB.
(37) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

***Scheme 12.*** Synthesis of Alcohol **63**[a]

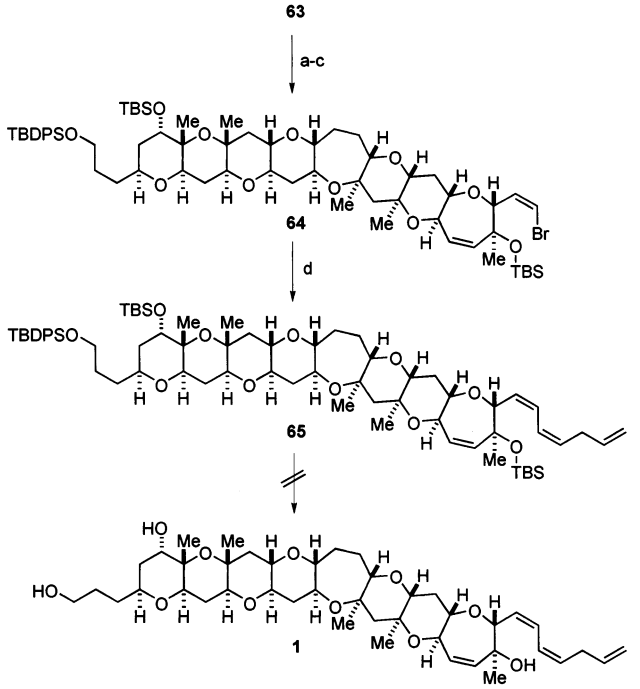



[a] Reagents and conditions: (a) NaOMe, 1:1 MeOH/$CH_2Cl_2$, rt. (b) TBSCl, imidazole, DMF, 0 °C. (c) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, rt, 69% (three steps). (d) LiHMDS, TMSCl, $Et_3N$, THF, −78 °C. (e) $Pd(OAc)_2$, MeCN, rt. (f) MeMgBr, toluene, −78 °C, 94% (three steps). (g) TBSOTf, $Et_3N$, $CH_2Cl_2$, rt. (h) LiDBB, THF, −78 → −45 °C. (i) TBDPSCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 99% (three steps). (j) TBSOTf, $Et_3N$, $CH_2Cl_2$, rt. (k) CSA, 1:1 MeOH/$CH_2Cl_2$, 0 °C, 93% (two steps).

afforded alcohol **62** (99% yield for the three steps). Further silylation of the C6 alcohol with TBSOTf and $Et_3N$ followed by selective removal of the TBS group at C32 led to alcohol **63** in 93% yield for the two steps.

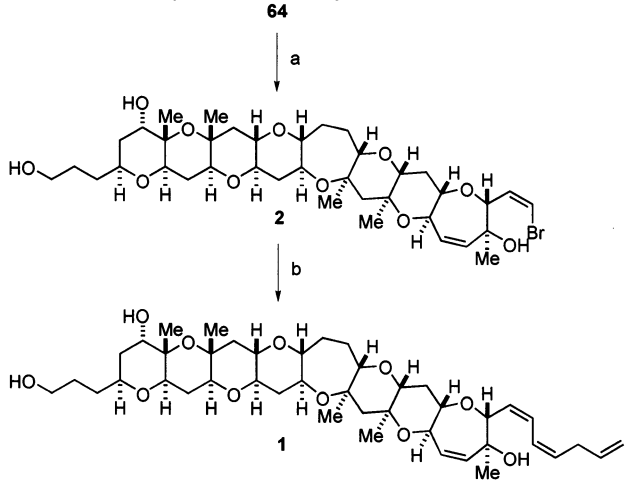
Alcohol **63** was then transformed by a three-step sequence as described before into dibromoolefin **64**, setting the stage for the introduction of the triene side chain (Scheme 13). The Stille coupling of **64** with (*Z*)-vinyl stannane **3** was carried out under the optimized conditions described before [$Pd(PPh_3)_4$, CuCl, LiCl, 1:1 DMSO/THF, 60 °C] to furnish fully protected gambierol **65** in 66% yield (82% yield based on recovered **64**).[38] Global silyl ether deprotection proved to be much more difficult than expected. The sterically hindered C30 TBS ether could not be cleaved under a variety of conditions, by TBAF, HF·pyridine, or tris(dimethylamino)sulfur difluorotrimethylsilicate (TASF).[39] Also, all attempts to cleave the C30 silyl group by extending the reaction time or forcing the reaction

***Scheme 13.*** Synthesis of Fully Protected Gambierol[a]




[a] Reagents and conditions: (a) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, rt. (b) $CBr_4$, $PPh_3$, $Et_3N$, $CH_2Cl_2$, 0 °C. (c) *n*-$Bu_3SnH$, $Pd(PPh_3)_4$, benzene, rt, 82% (three steps). (d) **3**, $Pd(PPh_3)_4$, CuCl, LiCl, 1:1 DMSO/THF, 60 °C, 66% (82% based on recovered **64**).

***Scheme 14.*** Completion of Total Synthesis of Gambierol[a]




[a] Reagents and conditions: (a) HF·pyridine, THF, rt, quant. (b) **3**, $Pd(PPh_3)_4$, CuCl, LiCl, 1:1 DMSO/THF, 60 °C, 43%.

conditions resulted in isomerization or loss of the labile triene moiety.

After extensive experimentation, it was found that exposure of (*Z*)-vinyl bromide **64** to excess HF·pyridine (THF, room temperature, 6 days) cleanly afforded triol **2** in quantitative yield. Finally, the Stille coupling of **2** with **3** under the established $Pd(PPh_3)_4$/CuCl/LiCl-promoted conditions (1:1 DMSO/THF, 60 °C) furnished (−)-gambierol (**1**) in 43% isolated yield (Scheme 14 ). The synthetic gambierol was identical to the natural sample by $^1H$ NMR, $^{13}C$ NMR, and HRMS spectra. Also, the CD spectra measured for synthetic **1** showed close agreement with that for the natural material. Moreover, mouse lethality of synthetic gambierol (ip, 50−75 $\mu$g/kg) was equipotent to that of the natural toxin. Thus, the structure of gambierol including

(38) In this reaction, (*Z*)-vinyl bromide **64** was not consumed completely, and an inseparable 4:1 mixture of **65** and **64** was obtained in 82% yield. The yield of **65** was estimated to be 66% by the $^1H$ NMR analysis of the purified mixture.

(39) (a) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, A. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

the absolute configuration was unambiguously confirmed as shown in Figure 1.

## Conclusion

We have achieved the first total synthesis of the marine polycyclic ether toxin gambierol. Efficient and practical synthetic routes to the ABC and EFGH ring fragments (**5** and **6**, respectively) allowed preparation of these advanced intermediates in multigram quantities. Convergent union of these key fragments has been successfully accomplished by utilizing our *B*-alkyl Suzuki−Miyaura coupling strategy, which realized a highly convergent synthesis of the octacyclic polyether core of gambierol. We are now confident that our strategy is feasible and powerful enough for the convergent synthesis of complex polycyclic ethers. We have also demonstrated the feasibility of the $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille conditions for the coupling of less reactive and sterically hindered (*Z*)-vinyl bromide and (*Z*)-vinyl stannane. The present total synthesis is highly convergent and flexible when one considers the structural complexity and size of the targeted molecule; its longest linear sequence from commercially available 2-deoxy-D-ribose consisted of 71 steps with an overall yield of 0.57%. The chemistry described herein would provide easy access to a variety of structural analogues of gambierol. Studies toward clarification of the biological profile of gambierol as well as preparation of its analogues are currently underway and will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds, $^1H$ and $^{13}C$ NMR spectra for selected compounds, and NMR and CD comparison data for natural and synthetic gambierol (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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