

Total Synthesis of Gambierol

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In recent years, there has been an explosion of interest in biologically active natural products of marine origin.¹ Because of 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.³ The compound shows toxicity against mice (LD₅₀ 50 µg/kg), and the symptoms resemble those caused by ciguater toxins, inferring the possibility that it is also implicated in ciguatera poisoning.¹ The unique structural features have attracted the attention of synthetic chemists, and a number of strategies have been investigated.^{4,5} In this paper, we describe a new approach to the total synthesis of gambierol (**1**).

Figure 1 illustrates our retrosynthetic analysis of **1**. Recently, we developed a convergent method for the synthesis of polycyclic ether frameworks via the intramolecular allylation of α -acetoxoxy ethers and subsequent ring-closing metathesis.^{4i,1} On the basis of this methodology, the octacyclic ether framework of **1** was retrosynthetically broken down into the ABC ring segment **3** and the FGH fragment **4** via the diene **2**.

The initial task of the total synthesis was the construction of the octacyclic framework. The carboxylic acid **3** and the alcohol **4**⁶ were connected by Yamaguchi conditions⁷ to give the ester **5** in 94% yield (Scheme 1). A series of reactions including desilylation with TBAF, acid-catalyzed acetal formation with **6**, and acetal cleavage with TMSI/HMDS furnished the allylic stannane **7** in 77% overall yield.⁸ The ester **7** was then subjected to the modified Rychnovsky acetylation. Thus, partial reduction of **7** with DIBALH, followed by treatment of the resulting aluminum hemiacetal with (CH₂ClCO)₂O/pyridine/DMAP,⁹ gave the α -chloroacetoxoxy ether **8** as a 3:2 inseparable mixture of diastereoisomers in 88% yield. Treatment of **8** with BF₃·OEt₂ gave a 2:1 mixture of the desired product **2** and its epimer **9** in 87% yield.^{10,11} The diene **2** obtained was subjected to ring-closing metathesis using the second generation Grubbs catalyst **10**¹² to give the octacyclic ether **11** in 88% yield.

We then focused on the modification of the H ring moiety. Hydrolysis of the benzylidene acetal of **11** led to the corresponding diol. Selective protection of the primary alcohol followed by TPAP oxidation of the secondary alcohol gave the ketone **12** in 77% overall yield. Hydrogenation of **12** followed by debenzoylation gave the saturated diol. The primary and secondary alcohols were protected by Pv and TIPS groups, respectively, to afford **13** in 80% overall yield. Treatment of **13** with LiHMDS/TMSCl/Et₃N⁵ gave the corresponding enol silyl ether, which was subjected to dehydrosilylation with Pd(OAc)₂¹³ to afford the enone **14** in 92% overall yield. Stereoselective introduction of the methyl group was carried out using MeMgI in toluene¹⁴ to give the tertiary alcohol

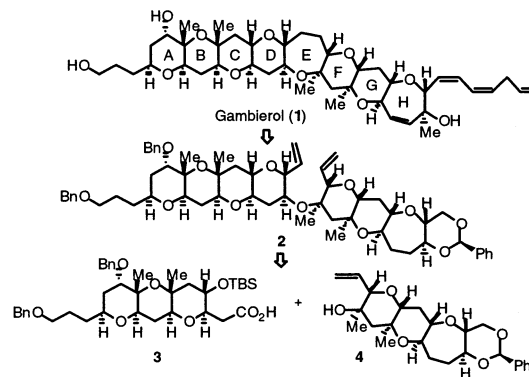


Figure 1. Retrosynthetic analysis of gambierol (**1**).

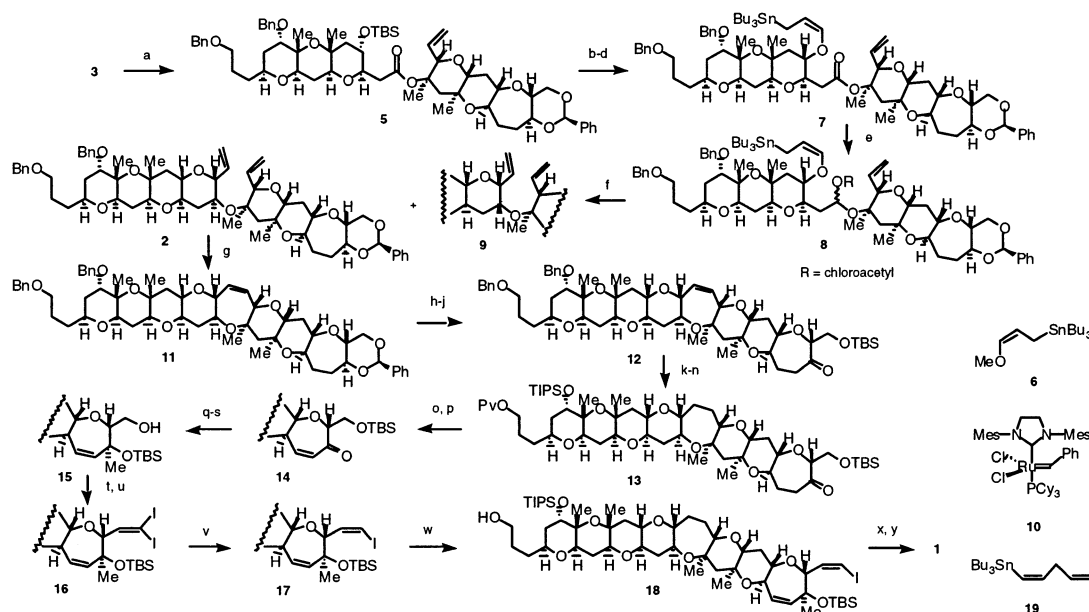
as a single stereoisomer. TBS protection and subsequent selective deprotection of the primary silyloxy group afforded **15** in 82% overall yield.

We have already succeeded in the stereoselective synthesis of the triene moiety via the Uenishi hydrogenolysis of dibromoalkene followed by a modified Stille coupling in a model study.^{4c} However, the coupling reaction of *Z*-bromoalkenes was very slow. This problem prompted us to develop an efficient method for the construction of the triene side chain. After several unfruitful attempts, we found that the reduction of diiodoalkenes with a Zn–Cu couple gave reactive *Z*-iodoalkenes in a highly stereoselective manner.¹⁵ Thus, PCC oxidation of **15** followed by treatment of the resulting aldehyde with Cl₄ and PPh₃¹⁶ gave the diiodoalkene **16** in 92% overall yield. Stereoselective hydrogenolysis of **16** was carried out by using a Zn–Cu couple and AcOH in THF–MeOH to give the *Z*-iodoalkene **17** as a single stereoisomer, which was then treated with DIBALH, furnishing **18** in quantitative yield. Deprotection of the bis-silyl ether **18** with SiF₄ proceeded smoothly to afford the corresponding triol.¹⁷ Finally, the iodoalkene obtained was subjected to the modified Stille coupling with **19** to give gambierol (**1**) in 72% yield.¹⁸ The synthetic gambierol exhibited physical and spectroscopic data identical to those reported previously.^{3,5}

In conclusion, the convergent total synthesis of gambierol has been achieved using the intramolecular allylation of α -chloroacetoxoxy ether and subsequent ring-closing metathesis. The longest linear sequence leading to **1** was 66 steps with 1.2% overall yield, and the total number of steps was 102, while the synthesis by Sasaki and Tachibana gave an overall yield of 0.57% by 71 steps, with a total of 107 steps.⁵ The present synthesis demonstrated that this methodology is efficient and practical for constructing polycyclic ether frameworks. Application of the present strategy to the synthesis of other marine natural products is in progress.

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Scheme 1^a

^a (a) 2,4,6-Trichlorobenzoyl chloride, Et₃N, THF, 40 °C, then **4**, DMAP, toluene, 40 °C, 94%; (b) TBAF, THF, room temperature, 99%; (c) **6**, CSA, CH₂Cl₂, room temperature; (d) HMDS, TMSI, CH₂Cl₂, 0 °C, 78% (two steps); (e) DIBALH, CH₂Cl₂, -78 °C, then (CH₂ClCO)₂O, DMAP, pyridine, -78 °C to room temperature, 88%; (f) BF₃·OEt₂, MS4A, CH₃CN, -40 to 0 °C, 87% (**2**:**9** = 2:1); (g) **10**, CH₂Cl₂, room temperature, 88%; (h) CSA, CH₂Cl₂-MeOH, 30 °C; (i) TBSCl, imidazole, CH₂Cl₂, 0 °C, 80% (two steps); (j) TPAP, NMO, MS4A, CH₂Cl₂, room temperature, 96%; (k) H₂, Pd-C, EtOAc, room temperature; (l) H₂, Pd(OH)₂-C, EtOAc, room temperature; (m) PvCl, DMAP, CH₂Cl₂, room temperature; (n) TIPSOTf, 2,6-lutidine, DMF, 65 °C, 80% (four steps); (o) LiHMDS, TMSI, Et₃N, THF, -78 °C; (p) Pd(OAc)₂, CH₃CN, 92% (two steps); (q) MeMgI, toluene, -78 °C; (r) TBSOTf, 2,6-lutidine, CH₂Cl₂, room temperature; (s) CSA, CH₂Cl₂-MeOH, 0 °C, 82% (three steps); (t) PCC, MS4A, CH₂Cl₂, room temperature; (u) Cl₄, PPh₃, CH₂Cl₂, 0 °C, 92% (two steps); (v) Zn-Cu, AcOH, THF-MeOH, 0 °C; (w) DIBALH, CH₂Cl₂, -78 °C, 100% (two steps); (x) SiF₄, CH₂Cl₂-CH₃CN, 0 °C; (y) **19**, Pd₂dba₃·CHCl₃, P(furyl)₃, CuI, DMSO, 40 °C, 72% (two steps).

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Supporting Information Available: Schemes for the preparation of compounds **3** and **4**. Experimental procedures and characterization data for all new compounds reported in Scheme 1. Copies of ¹H 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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- (18) Fuji Silysia silica gel was used for the purification of **1**. Although the detail is not clear, the use of Kanto Chemical silica gel (neutral) caused partial isomerization of **1**. See Supporting Information.

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