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Synthetic studies on a marine polyether toxin, gambierol: stereoselective synthesis of the FGH ring system via *B*-alkyl Suzuki coupling

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Abstract

A synthetic route to the FGH ring system of gambierol, a marine polyether toxin isolated from the dinoflagellate *Gambierdiscus toxicus*, has been developed. The present synthesis features *B*-alkyl Suzuki coupling of the F and H rings, followed by ring-closure of the G ring and stereoselective installation of 1,3-diaxial methyl groups at C21 and C23. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: coupling reactions; polyethers; Suzuki reactions; toxins.

Gambierol (**1**) was isolated as a toxic constituent from the ciguatera causative dinoflagellate, *Gambierdiscus toxicus* and showed toxicity against mice (LD_{50} 50 μg/kg, mice, i.p.).[1] The mice symptoms resemble those shown by ciguatoxins, implying the possibility that it is also implicated in ciguatera fish poisoning, which is one of the most widespread seafood poisonings. Complete stereochemical assignments have been accomplished by extensive NMR analysis[1] and application of a chiral anisotropic reagent.[2] Its characteristic polyether structure, potent biological activity, and extremely limited availability from natural sources make gambierol an intriguing synthetic target molecule.[3] We have recently reported a new methodology for the convergent assembly of a polyether structure utilizing *B*-alkyl Suzuki coupling of lactone-derived enol phosphates and disclosed its potential in the synthesis of ciguatoxin fragments.[4] In this letter, we describe a stereocontrolled construction of the FGH ring system (**2**) of gambierol based on the *B*-alkyl Suzuki coupling strategy.[5]

A convergent synthetic approach to gambierol (**1**) involves construction of two fragments representing the ABC and EFGH ring systems. The latter compound was to be derived from the precursor FGH ring system (**2**). Our strategy for the synthesis of **2** was based on *B*-alkyl Suzuki

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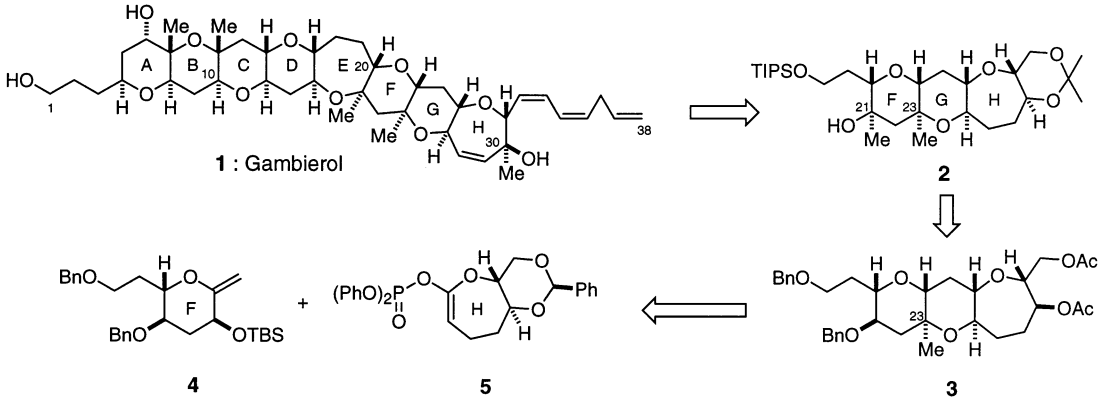
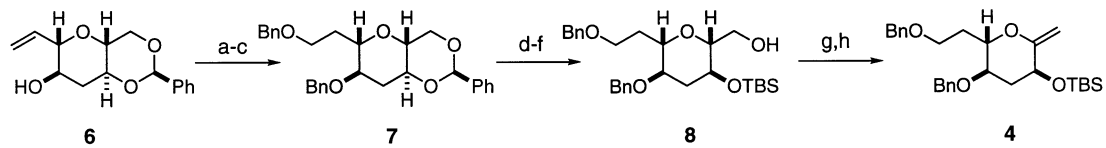
coupling of the F and H ring precursors and then ring-closure of the G ring (Scheme 1; **4**+**5**→**3**). A formidable challenge in synthesizing **2** appeared to be the introduction of the 1,3-diaxial dimethyl groups at C21 and C23 positions on the F ring. We could solve the problem by a preliminary introduction of the C23 methyl group, followed by installation of a quaternary center at C21 (**3**→**2**).



Scheme 1.

Synthesis of *exo*-olefin **4** started with alcohol **6**,[6] which was converted into bis(benzyl)ether **7** by a three-step procedure involving protection as the benzyl ether, hydroboration-oxidation, and benzylation. Following removal of the benzylidene acetal, the resultant diol was converted into alcohol **8** by silylation of both hydroxyl groups and subsequent selective mono-desilylation. Iodination of **8**, followed by base treatment provided the desired *exo*-olefin **4** (Scheme 2).



Scheme 2. Reagents and conditions: (a) NaH, BnBr, Bu_4NI, DMF, rt, 97%; (b) 9-BBN, THF, rt, then H_2O_2, NaOH, rt, 95%; (c) KH, BnBr, Bu_4NI, THF, reflux, 76%; (d) *p*-TsOH, MeOH–CH_2Cl_2, rt, 86%; (e) TBSCl, imidazole, DMF, 50°C; (f) CSA, MeOH–CH_2Cl_2, 0°C, 96% (two steps); (g) I_2, PPh_3, imidazole, benzene, rt, 95%; (h) KO–*t*-Bu, THF, 0°C, 96%

In our previous *B*-alkyl Suzuki coupling,[4b,c] excess amounts (2 equiv.) of the phosphate coupling partners and elevated reaction temperature were required to realize the coupling reaction in high yield. These problems prompted us to explore the optimum reaction conditions for the hydroboration-Suzuki coupling of **4** and **5**. Hydroboration of the *B*-alkyl Suzuki coupling partner **4** and direct subjection of the resultant alkylborane to enol phosphate **5** under the previously reported conditions (aqueous 1 M $NaHCO_3$ (3 equiv.), $Pd(PPh_3)_4$ (10 mol%), DMF, 50°C)[4b] afforded cross-coupled product **9** in 87% yield (Table 1, entry 1). Use of $PdCl_2$(dppf) (dppf = 1,1′-bis(diphenylphosphino)ferrocene) as a catalyst improved the yield of **9** (entry 2) and allowed the coupling reaction to proceed at room temperature in high yield (entry 3).[7] On the other hand, use of $PdCl_2(PCy_3)_2$[8] with an electron-rich ligand lowered the yield of the coupling reaction (entry 4).[9] It has recently been reported that $Pd(OAc)_2$/*o*-(di-*tert*-butylphosphino)biphenyl efficiently promotes the room temperature Suzuki coupling of aryl chlorides;[7e,f] however, this catalyst system was also less effective in the present case (entry 5).

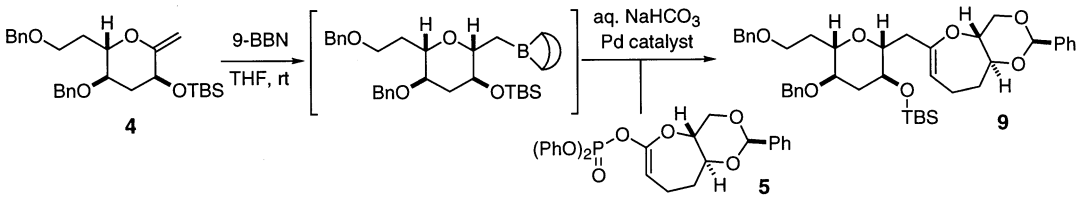


Table 1[a]

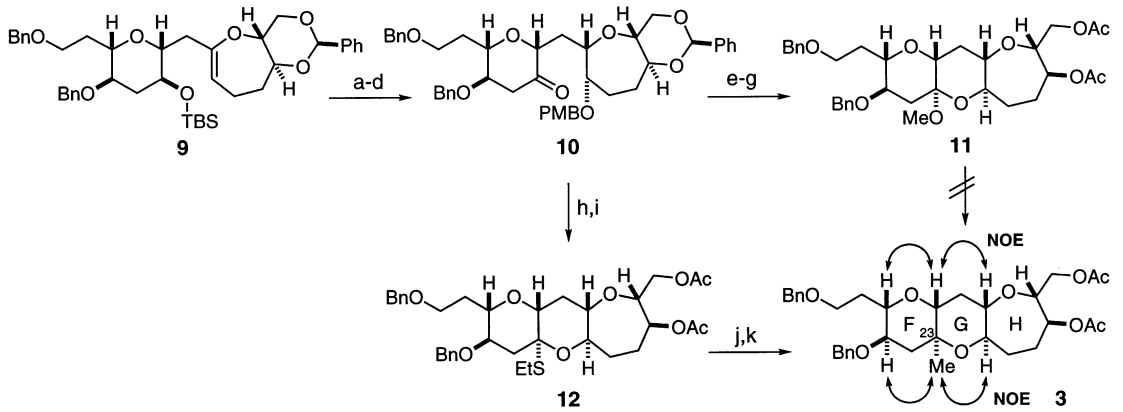
Run	Catalyst	Conditions	% Yield
1	$Pd(PPh_3)_4$	DMF, 50°C, 20 h	87
2	$PdCl_2$(dppf)	DMF, 50°C, 20 h	93
3	$PdCl_2$(dppf)	DMF, rt, 24 h	97
4	$PdCl_2(PCy_3)_2$	DMF, 50°C, 20 h	50
5[b]	$Pd(OAc)_2$/ 	Dioxane, rt, 24 h	58

[a] Reactions were carried out using 10 mol% of Pd catalyst, 3 equiv. of base, and 1.2 equiv. of **5**; reaction times have not been minimized.

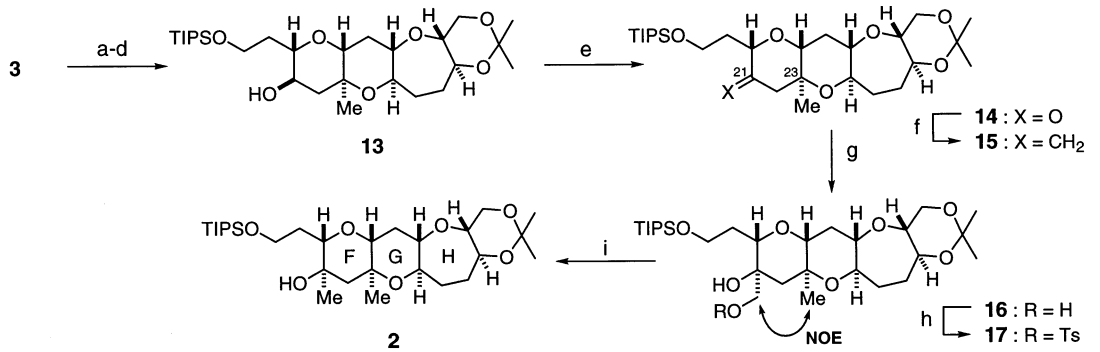
[b] 20 mol% of ligand was used.

Ring-closure of the G ring and installation of the C23 angular methyl group is summarized in Scheme 3. Hydroboration of **9** with BH_3·THF, followed by oxidative workup proceeded stereoselectively to give an alcohol (77%),[10] which was then protected as the *p*-methoxybenzyl (PMB) ether. Desilylation and oxidation of the resultant alcohol with TPAP/NMO[11] provided ketone **10** in 83% yield for the three steps. We first attempted to install an angular methyl group at C23[12] via nucleophilic attack to an oxocarbenium ion generated from methyl acetal **11**. Removal of the PMB group, followed by methyl acetal formation and acetylation afforded **11** as a single stereoisomer. However, upon treatment of **11** with Me_3Al or Me_2Zn in the presence of BF_3·OEt_2,[13] none of the desired methylated product **3** was obtained. Thus, ketone **10** was transformed into hemithioketal **12**. Following removal of the PMB group, treatment of the resulting hemiacetal with EtSH and $Zn(OTf)_2$[14] and in situ acetylation provided **12** in 86% overall yield. Oxidation of **12** to the corresponding sulfone and subsequent reaction with Me_3Al[15] led exclusively to the desired **3** in 86% overall yield. The relative configuration of **3** was unambiguously established by NOE experiments, as shown in Scheme 3.

Final installation of the quaternary carbon center at C21 could be accomplished, as shown in Scheme 4. Routine protective group manipulation allowed for transformation of **3** into alcohol **13**, which was then oxidized with TPAP/NMO to give ketone **14**. Initial attempts to introduce a methyl group at C21 by nucleophilic addition were unsuccessful, and the undesired β-methyl isomer was obtained as the major product due to the serious steric congestion of the angular methyl group at C23. However, dihydroxylation of *exo*-olefin **15**, derived from **14** by Wittig reaction, afforded diol **16** as a single stereoisomer in high yield.[16] In this reaction, excess amounts of OsO_4 (3 equiv.) and NMO (10 equiv.) were required to obtain a high yield of **16**. Selective tosylation of the primary hydroxyl group in **16** gave monotosylate **17**, where the



Scheme 3. Reagents and conditions: (a) BH_3·THF, THF, −30°C; then H_2O_2, NaOH, rt→40°C, 77%; (b) KH, PMBCl, Bu_4Nl, THF, rt, 88%; (c) Bu_4NF, THF, rt, quant.; (d) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 94%; (e) DDQ, CH_2Cl_2–phosphate buffer (pH 7), rt; (f) *p*-TsOH·H_2O, $CHCl_3$–MeOH, rt, 82% (two steps); (g) Ac_2O, DMAP, CH_2Cl_2, 0°C, 97%; (h) DDQ, CH_2Cl_2–phosphate buffer (pH 7), rt; (i) EtSH, $Zn(OTf)_2$, $NaHCO_3$, CH_2Cl_2, rt; then Ac_2O, Et_3N, DMAP, 86% (three steps); (j) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 96%; (k) Me_3Al, CH_2Cl_2, −78°C, 90%



Scheme 4. Reagents and conditions: (a) NaOMe, MeOH, rt; (b) $Me_2C(OMe)_2$, PPTS, DMF, rt, 98% (two steps); (c) H_2, $Pd(OH)_2$/C, EtOAc, rt; (d) TIPSCl, imidazole, CH_2Cl_2, rt, 89% (two steps); (e) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 99%; (f) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, −78°C→rt, 92%; (g) OsO_4 (3 equiv.), NMO (10 equiv.), *t*-BuOH–H_2O (1:1), rt, 96%; (h) TsCl, DMAP, $(CH_2Cl)_2$, rt, 99%; (i) $LiAlH_4$, THF, 0°C→rt, 75%

stereochemistry at C21 was established by NOE experiment. Finally, reduction of **17** with $LiAlH_4$ at 0°C yielded the corresponding epoxide, which upon warming to room temperature delivered the desired FGH ring system **2** in 75% yield.[17,18]

In conclusion, we have completed the synthesis of the FGH ring system of gambierol. In the present synthesis we have demonstrated that $PdCl_2$(dppf) promotes the room temperature *B*-alkyl Suzuki coupling of lactone-derived enol phosphate. The mild reaction conditions described herein should tolerate the presence of a wide variety of functional groups and thus enhance the practicality and usefulness of the *B*-alkyl Suzuki coupling strategy for the synthesis of a polyether system. Also, 1,3-diaxial dimethyl groups with serious steric congestion were successfully introduced. Further efforts directed toward a total synthesis of gambierol are underway and will be reported in due course.

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16. Epoxidation of **15** with *m*CPBA (Na_2HPO_4, 4,4′-thiobis(6-*t*-butyl-*m*-cresol), $ClCH_2CH_2Cl$ or toluene, 90°C) provided the corresponding epoxide in poor selectivity (α-epoxide and β-epoxide = 2:3).
17. $LiAlH_4$ reduction of **17** at 0°C gave the corresponding epoxide in 92% yield.
18. Selected data for compound **2**: ^{1}H NMR (500 MHz, C_6D_6) δ 3.94–3.86 (m, 2H, 18-H, 32-H), 3.84 (m, 1H, 18-Hr), 3.71 (m, 1H, 30-H), 3.64 (dd, 1H, J = 11.3, 8.93 Hz, 32-H), 3.51–3.46 (m, 2H, 20-H, 27-H), 3.24 (ddd, 1H, J = 8.9, 8.9, 5.5 Hz, 31-H), 3.07 (dd, 1H, J = 12.8, 4.0 Hz, 24-H), 3.02 (ddd, 1H, J = 11.0, 9.2, 5.2 Hz, 26-H), 2.17 (ddd, 1H, J = 11.6, 5.2, 4.0 Hz, 25-H), 2.05–1.90 (m, 4H, 19-H, 22-H, 28-H, 29-H), 1.84–1.66 (m, 5H, 22-H, 25-H, 28-H, 29-H, OH), 1.62 (m, 1H, 19-H), 1.60 (s, 3H, acetonide), 1.45 (s, 3H, acetonide), 1.18–1.03 (m, 27H, 41-Me, 42-Me, Si*CHMe*$_2$×3); ^{13}C NMR (125 MHz, C_6D_6) δ 98.4, 85.1, 80.5, 76.0, 73.2, 73.1, 72.0, 70.1, 63.5, 61.1, 54.6, 33.1, 32.5, 30.2, 29.8, 28.8, 24.7, 19.5, 18.2, 15.8, 12.3; HRMS (FAB) calcd for $C_{29}H_{54}O_7SiNa$ [(M+Na)$^+$] 565.3537, found 565.3527.