ORGANIC LETTERS

2002
Vol. 4, No. 17
2981−2984

Total Synthesis of Gambierol

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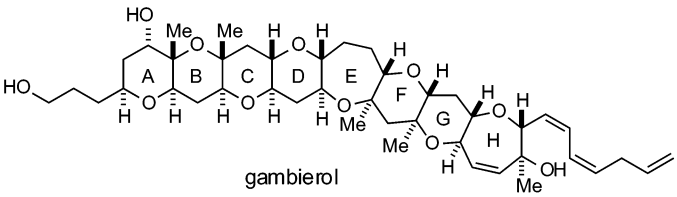
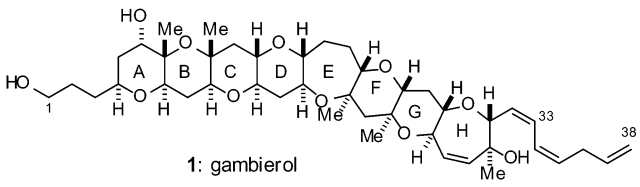
Received June 20, 2002

ABSTRACT



The first total synthesis of gambierol, a marine polycyclic ether toxin, has been achieved. The synthesis features the Pd(PPh$_3$)$_4$/CuCl/LiCl-promoted Stille coupling for the stereoselective construction of the sensitive triene side chain that includes a conjugated (*Z*,*Z*)-diene moiety.

The fused polcyclic ether class of marine natural products, exemplified by brevetoxins, ciguatoxins, and maitotoxin, has received much attention due to the structural complexity and biological potency of these molecules.[1,2] Gambierol (**1**) is a marine polycyclic ether isolated as a toxic constituent from cultured cells of the ciguatera causative dinoflagellate, *Gambierdiscus toxicus*. The gross structure and relative stereochemistry have been established by Yasumoto and co-workers on the basis of extensive NMR studies,[3] and subsequently, the absolute configuration was determined by an application of a chiral anisotropic reagent.[4] Gambierol exhibits potent toxicity against mice at 50 μg/kg (ip), and the symptoms caused in mice resemble those shown for ciguatoxins,[5] the principal toxins responsible for ciguatera, which is a very widespread seafood poisoning. This finding implies that gambierol is also implicated in ciguatera fish poisoning. However, the biological basis of the potent toxicity remains unknown mainly due to its limited availability from natural sources. Its polycyclic ether structure including a characteristic triene side chain, as well as its biological profile, has inspired a number of efforts toward its synthesis.[6,7] We have previously reported a highly convergent synthesis of the octacyclic polyether core **2** of gambierol by extensive use of the *B*-alkyl Suzuki−Miyaura coupling reaction.[6c] Herein we describe the first total synthesis of gambierol, featuring the stereoselective construction of a highly sensitive triene side chain via the Pd(PPh$_3$)$_4$/CuCl/LiCl-promoted Stille coupling.



The presence of a partially skipped triene side chain that includes a conjugated (*Z*,*Z*)-diene system represents a formidable synthetic challenge for the completion of the total synthesis of gambierol. A modified Stille coupling protocol for the C33−C34 bond formation reported as a model study

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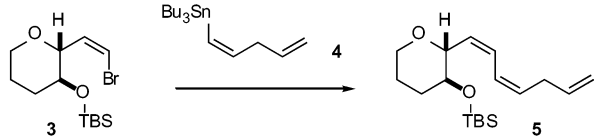
10.1021/ol026394b CCC: $22.00
Published on Web 07/19/2002

Table 1. Stille Coupling of (*Z*)-Vinyl Bromide **3** and (*Z*)-Vinyl Stannane **4**[a]



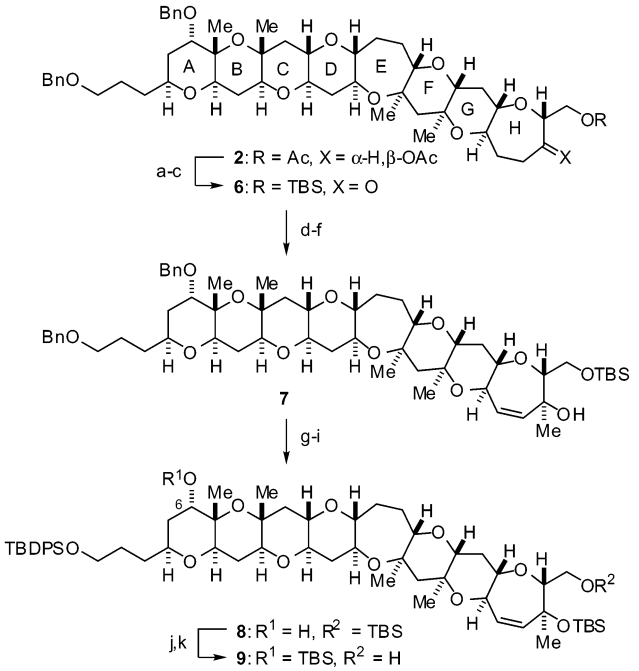
entry	Pd(0)	ligand[b]	cocatalyst[c] (equiv)	additive (equiv)	temp	yield
1	$Pd_2(dba)_3{\cdot}CHCl_3$	TFP	CuI (1.6)		rt	49[d]
2	$Pd_2(dba)_3{\cdot}CHCl_3$	TFP	CuI (10)		60 °C	50
3	$Pd_2(dba)_3{\cdot}CHCl_3$	TFP	CuTC (10)		60 °C	69
4	$Pd_2(dba)_3{\cdot}CHCl_3$	TFP	CuTC (10)		rt	75
5	$Pd(PPh_3)_4$		CuCl (10)	LiCl (12)	rt	49[d]
6	$Pd(PPh_3)_4$		CuCl (10)	LiCl (12)	60 °C	81

[a] All reactions were carried out using **3** (1 equiv) and **4** (2 equiv) in the presence of Pd(0) catalyst (20 mol %) and ligand (80 mol %) in 1:1 v/v THF/DMSO for 2 days. [b] TFP = (2-furyl)$_3$P. [c] TC = thiophene-2-carboxylate. [d] Vinyl bromide **3** was not consumed completely, and the yield was estimated by ^{1}H NMR analysis of an inseparable mixture of **3** and **5**.

by Kadota, Yamamoto, and co-workers[7c] is a promising candidate for the construction of the triene side chain. However, an initial attempt to bring about the coupling of model substrate (*Z*)-vinyl bromide **3**[8] with (*Z*)-vinyl stannane **4**[9] in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$, (2-furyl)$_3$P, and CuI in THF/DMSO[10] afforded the desired cross-coupled product **5** in only a modest yield (Table 1, entries 1 and 2). Therefore, we reinvestigated the conditions to establish the optimal conditions for the cross-coupling reaction.[11] Use of copper(I) thiophene-2-carboxylate (CuTC)[12] accelerated the reaction and improved the yield of **5** (entries 3 and 4). Furthermore, the $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille conditions developed by Corey and co-workers[13] worked well in this reaction. Thus, the reaction of **3** and **4** with $Pd(PPh_3)_4$ (20 mol %), 10 equiv of CuCl, and 12 equiv of LiCl in 1:1 THF/DMSO at 60 °C afforded **5** in a gratifying 81% yield (entry 6). Notably, under these conditions, the cross-coupling reaction proceeded with complete retention of olefin stereochemistry.

Having established reliable conditions for the construction of the sensitive triene side chain, we proceeded forward to complete the total synthesis. Removal of the acetyl groups of **2** followed by selective silylation of the primary alcohol and oxidation of the residual secondary alcohol with TPAP/NMO[14] led to ketone **6** in 69% overall yield (Scheme 1).

Scheme 1. Synthesis of Alcohol **9**[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, CH_2Cl_2, THF, −78 °C. (e) $Pd(OAc)_2$, acetonitrile, 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).

Treatment of **6** with LiHMDS in the presence of TMSCl and Et_3N gave the corresponding enol silyl ether, which upon exposure to $Pd(OAc)_2$ in CH_3CN delivered enone.[15] Subsequent Grignard reaction (MeMgBr, toluene, −78 °C)[16]

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(8) The corresponding vinyl iodide was too unstable to be used.

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(10) A mixed solvent system of 1:1 THF/DMSO was used in the present study due to the low solubility of vinyl stannane **4** in DMSO.

(11) In the absence of copper(I) salt, the yield of Stille product **5** was very low.

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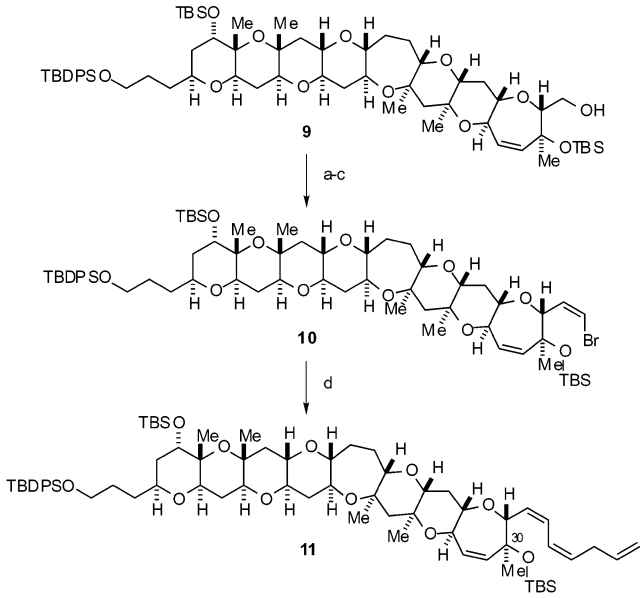
(16) Feng, F.; Murai, A. *Chem. Lett.* **1992**, 1587−1590.

afforded tertiary alcohol **7** in 94% overall yield as a single diastereomer. After protection as its TBS ether, the benzyl groups were reductively removed with LiDBB (THF, −78 → −45 °C),[17] and the resulting diol was selectively protected as the *tert*-butyldiphenylsilyl (TBDPS) ether **8** in high overall yield. Further silylation of the C6 alcohol and selective removal of the primary TBS group led to alcohol **9** in 93% yield over two steps.

Oxidation of **9** with TPAP/NMO followed by Corey−Fuchs reaction[18] provided dibromoolefin, which was stereoselectively reduced with *n*-Bu_3SnH and $Pd(PPh_3)_4$[19] to deliver (*Z*)-vinyl bromide **10** in 82% overall yield, setting the stage for the crucial Stille coupling (Scheme 2). As expected, cross-

Scheme 2. Synthesis of Fully Protected Gambierol **11**[a]

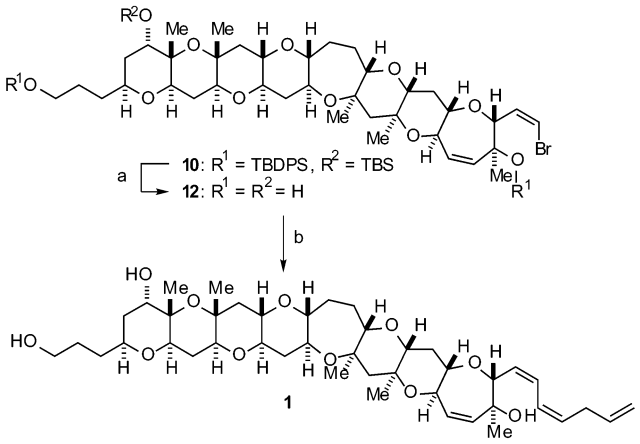


[a] Reagents and conditions: (a) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt. (b) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0 °C. (c) *n*-Bu_3SnH, $Pd(PPh_3)_4$, benzene, rt, 82% (three steps). (d) **4**, $Pd(PPh_3)_4$, CuCl, LiCl, 1:1 DMSO/THF, 60 °C, 43 h, 66%.

coupling of the sterically congested vinyl bromide **10** with **4** was effected under the optimal conditions described above, giving rise to fully protected gambierol **11** with complete retention of olefin stereochemistry.[20]

For completion of the total synthesis of **1**, there remained only removal of the silyl protective groups. However, global silyl ether deprotection proved to be problematic. The C30

Scheme 3. Total Synthesis of Gambierol (**1**)[a]



[a] Reagents and conditions: (a) HF·pyridine, THF, rt, quant. (b) **4**, $Pd(PPh_3)_4$, CuCl, LiCl, 1:1 DMSO/THF, 60 °C, 2 days, 43%.

TBS ether could not be removed under a variety of conditions, using TBAF, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF),[21] or HF·pyridine. Furthermore, undesired side reactions that resulted in isomerization or loss of the highly labile triene moiety could not be suppressed. After extensive investigations, it was found that treatment of vinyl bromide **10** with excess HF·pyridine (THF, room temperature, 6 days) cleanly afforded triol **12** in quantitative yield. Finally, cross-coupling of **12** with **4** under the described $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille conditions proceeded stereoselectively to furnish gambierol **1** in 43% isolated yield. The synthetic gambierol was completely identical to the natural sample by ^1H and ^{13}C NMR spectra; thus, the structure of gambierol was unambiguously confirmed. Moreover, mouse lethality of synthetic gambierol (ip, 50−75 μg/kg) was comparable to that of the natural sample.

In summary, the first total synthesis of gambierol (**1**) has been achieved. The $Pd(PPh_3)_4$/CuCl/LiCl-promoted Stille coupling process has been successfully applied to the stereoselective synthesis of the sensitive triene side chain that includes a conjugated (*Z*,*Z*)-diene. Careful choice of the global deprotection stage was found to be crucial for the success of the present total synthesis. The described chemistry provides easy access to structural analogues of gambierol for further study, including biological evaluation. Further investigation along these lines is currently under way and will be reported in due course.

Acknowledgment. This work was financially supported in part by a grant from Suntory Institute for Bioorganic Research (SUNBOR). A fellowship (to H.F.) from the Japan Society for the Promotion of Science is also gratefully acknowledged.

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(20) In this reaction, vinyl bromide **10** was not consumed completely and an inseparable 4:1 mixture of **11** and **10** was obtained in 82% yield. The yield of **11** was estimated to be 66% by the ^1H NMR analysis of the purified mixture.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5** and **1** and ^{1}H and ^{13}C NMR spectra for synthetic gambierol. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026394B