Diverted Total Synthesis and Biological Evaluation of Gambierol Analogues: Elucidation of Crucial Structural Elements for Potent Toxicity

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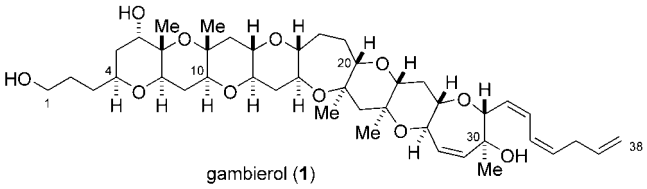
Abstract: Gambierol is a polycyclic ether toxin, which has been isolated from the marine dinoflagellate *Gambierdiscus toxicus*. A series of gambierol analogues have been prepared from an advanced intermediate of our total synthesis of gambierol and investigated for their toxicity against mice, thus providing the first systematic structure–activity relationships (SAR) of this polycyclic ether class of marine toxin. The SAR studies described herein clearly indicate that 1) the C28=C29 double bond within the H ring and the unsaturated side chain are the crucial structural elements required for exerting potent biological activity and 2) the C1 and C6 hydroxy groups, the C30 methyl group, and the C37=C38 double bond have little influence on the degree of neurotoxicity against mice.

Keywords: ciguatoxins · gambierol · polycyclic ethers · structure–activity relationships · total synthesis

Introduction

The fused polycyclic ether class of marine natural products has attracted the attention of chemists and biologists owing to their complex and large molecular architecture as well as their potent and diverse biological activities.[1] Ciguatoxin and its congeners, produced by the epiphytic dinoflagellate, *Gambierdiscus toxicus*, are a representative family of marine polycyclic ether toxins.[2,3] Ciguatoxins (CTXs) are the principal toxins responsible for the ciguatera seafood poisoning prevalent in the circumtropic area, from which more than 25000 patients suffer annually.[4] CTXs are known to exert their potent neurotoxicity by binding to voltage-sensitive sodium channels (VSSC) and altering their function.[5]

Gambierol (**1**) is another marine polycyclic ether toxin, which was isolated along with ciguatoxin congeners from culture cells of *G. toxicus* collected from the Rangiroa Peninsula in French Polynesia. Its gross structure including the relative stereochemistry has been determined by extensive NMR studies.[6] Subsequently, the absolute configuration



gambierol (**1**)

was established by derivatization and application of a modified Mosher analysis.[7] This intriguing toxic molecule consists of a *trans*-fused octacyclic polyether core that contains 18 stereogenic centers and a partially conjugated triene side chain, including a conjugated (*Z*,*Z*)-diene system, and thus it provides a formidable synthetic challenge. Gambierol exhibits potent neurotoxicity against mice with a minimal lethal dose (MLD) of 50 $\mu g\,kg^{-1}$ by intraperitoneal (ip) injection, and the neurological symptoms caused in mice resemble those shown by CTXs. This finding implies the possibility that gambierol is also responsible for ciguatera seafood poisoning. Very recently, Inoue et al. reported that gambierol inhibits the binding of dihydrobrevetoxin B (PbTx-3) to VSSC, though its binding affinity is significantly

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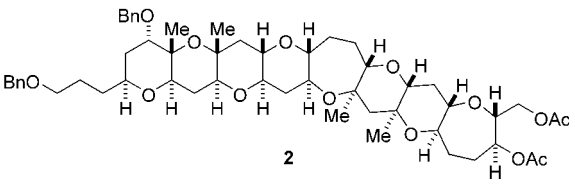
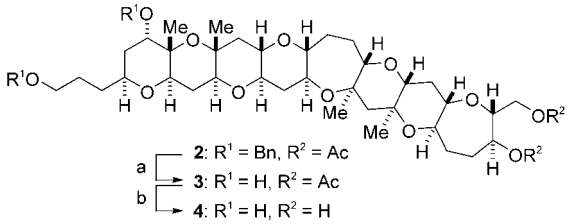
lower than those of brevetoxins and ciguatoxins.[8] Over the past decade, however, its extremely limited availability from nature has precluded detailed biological studies on this neurotoxin. Therefore, there have been strong demands for a supply of useful quantities of this natural product to be prepared by chemical total synthesis. Consequently, substantial efforts have been devoted towards the synthesis of gambierol[9] and, to date, two complete total syntheses have been reported by us[10] and by Yamamoto and co-workers.[11] Now that ample quantities of gambierol can be supplied by chemical synthesis, we undertook studies aimed at gaining an understanding of the molecular basis of the biological mode of action of this marine toxin. In this context, we have investigated the structure–activity relationships (SAR) of gambierol to establish the structural elements that are essential for potent biological activity and the basis for the design and synthesis of molecular probes useful for biological studies. Herein, we describe in detail the total synthesis and biological evaluation of a series of gambierol analogues, which culminated in the elucidation of the crucial structural elements required for potent neurotoxicity.[12]

Results and Discussion

Only a few reports concerning the structure–activity relationships (SAR) of marine polycyclic ether toxins exist.[13] Two plausible reasons for this are 1) the extremely limited availability of these secondary metabolites from natural sources and 2) the difficulties of altering the highly complex and huge molecular structures by chemical means. In the case of gambierol, we have solved the former problem by our convergent total synthesis, which realized the preparation of ample quantities of this natural toxin. However, owing to the presence of extremely sensitive functional groups, including the labile triene side chain and the tertiary allylic alcohol, the controlled chemical modification of gambierol itself is seemingly quite difficult.[7] On the other hand, information gained through the total synthesis suggested that one would be able to overcome such a limitation by carrying out analogue synthesis, starting from an advanced intermediate that has a simple structure and sufficient functional groups for further chemical manipulation.[14] During the course of our total synthesis of gambierol, we established a practical synthetic entry to the octacyclic polyether core **2**[9k,10] based on our modified Suzuki–Miyaura coupling approach.[15,16] This advanced intermediate fulfilled the above requirements and is available in a gram quantity. Thus, we anticipated that the octacyclic polyether core **2** would be an ideal starting point for the diverted total synthesis of gambierol analogues for SAR studies.

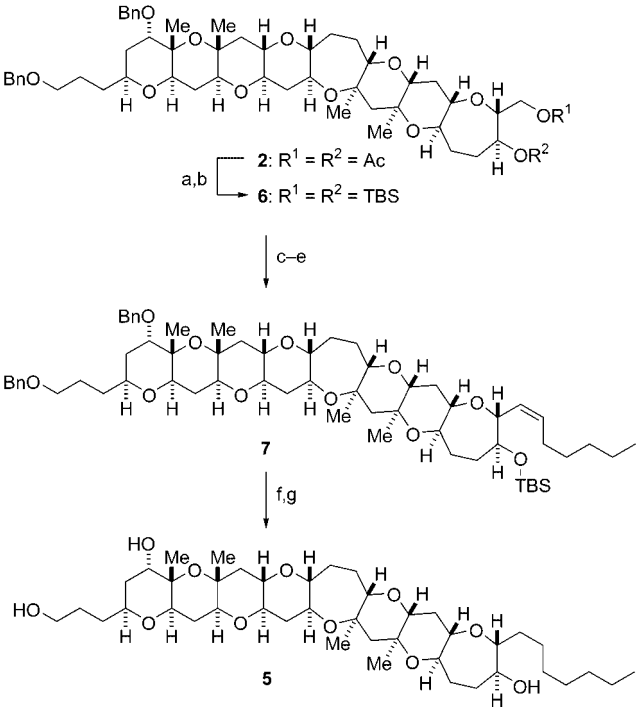


Synthesis of the right-wing modified analogues: We first directed our attention to the synthesis of the right-wing modified analogues of gambierol in order to evaluate the role of the H-ring functionalities and the lipophilic triene side chain. At the outset, we prepared analogues **3** and **4** to see whether the octacyclic polyether core of **1** alone is a sufficient minimal structure for exhibiting toxicity. Debenzylation of **2** by hydrogenolysis gave diol **3** in 94% yield (Scheme 1). Subsequent removal of the acetyl groups under



Scheme 1. Reagents and conditions: a) H_2, 20% $Pd(OH)_2$/C, EtOAc, RT, 94%; b) K_2CO_3, MeOH, RT, 84%.

basic conditions afforded tetraol **4** in 84% yield. We also synthesized analogue **5**, which bears a heptyl side chain (Scheme 2). Removal of the acetyl groups of **2** followed by silylation with *tert*-butyldimethylsilyl trifluoromethanesulfo-



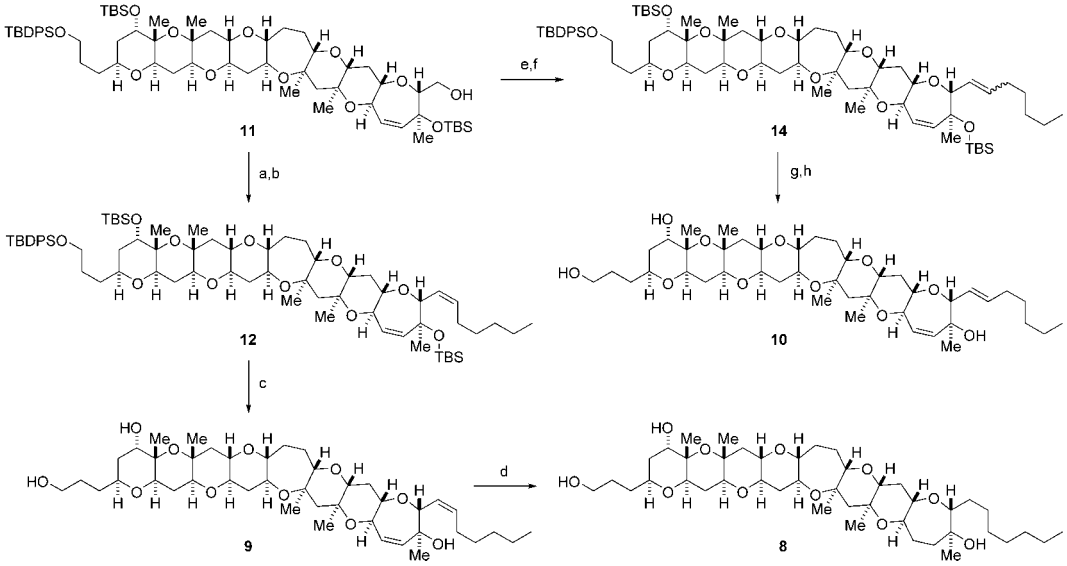
Scheme 2. Reagents and conditions: a) K_2CO_3, MeOH, RT; b) TBSOTf, Et_3N, DMF, 0°C; c) CSA, MeOH/CH_2Cl_2 (1:1), 0°C, 59% (three steps); d) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, RT; e) $Br^-Ph_3P^+(CH_2)_5CH_3$, NaHMDS, THF, 0°C, 45% (two steps); f) HF·pyridine, THF, RT, 72%; g) H_2, 20% $Pd(OH)_2$/C, MeOH/EtOAc (1:1), RT, quantitative. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; DMF = *N*,*N*-dimethylformamide; CSA = *dl*-camphorsulfonic acid; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide; NaHMDS = sodium bis(trimethylsilyl)amide.

nate (TBSOTf) and triethylamine led to the bis-silyl ether **6**. Selective liberation of the C32[17] primary hydroxy group under acidic conditions produced the alcohol in 59% yield for the three steps. Oxidation of the alcohol using Ley's conditions [tetra-*n*-propylammonium perruthenate (TPAP), *N*-methylmorpholine *N*-oxide (NMO)][18] and the ensuing Wittig reaction with the ylide generated from *n*-hexyltriphenylphosphonium bromide [$Br^-Ph_3P^+(CH_2)_5CH_3$], afforded (*Z*)-olefin **7** in 45% overall yield. Deprotection of the silyl group with HF·pyridine followed by removal of the benzyl groups with concomitant reduction of the double bond furnished analogue **5** in 72% yield for the two steps.

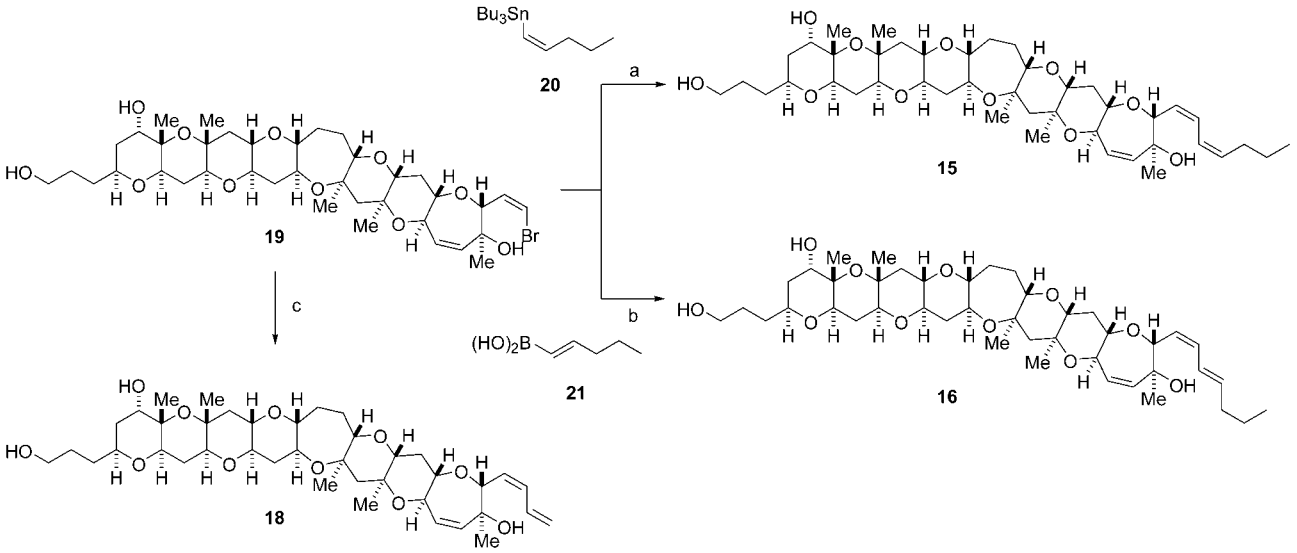
Analogues **8**--**10**, which possess the C30 axial methyl group, were prepared as depicted in Scheme 3. The synthesis of analogues **8** and **9** started from alcohol **11**, which is available in 11 steps from **2**.[10] Parikh–Doering oxidation of **11** and Wittig reaction of the derived aldehyde led to (*Z*)-olefin **12** in 58% overall yield. Removal of the silyl protecting groups by exposure to excess HF·pyridine furnished 34,35,37,38-tetrahydrogambierol (**9**) in 81% yield. Hydrogenation of **9** then afforded perhydrogambierol (**8**) in 59% yield. The synthesis of analogue **10** also commenced with alcohol **11**. Oxidation of **11** followed by Julia–Kociensky olefination[19] with a sulfone anion derived from 5-(pentane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**13**) gave olefin **14** as an inseparable mixture of geometric isomers with disappointingly poor selectivity (*E*:*Z* = ca. 1:2, 70% overall yield). Several attempts to improve the selectivity met with failure. However, after deprotection of the silyl groups by treatment with excess HF·pyridine, pure (32*E*)-34,35,37,38-tetrahydrogambierol (**10**) was isolated by HPLC separation of the configurational isomers.

To further investigate the effect of the multiunsaturated side chain of parent **1**, two isomeric diene analogues **15** and **16** and (32*E*)-analogue **17** as well as the truncated analogue **18** were designed. Analogues **15** and **16** were synthesized stereoselectively by palladium(0)-mediated cross-coupling[20] of (*Z*)-vinyl bromide **19**, accessible from **2** in 15 steps,[10] with (*Z*)-vinylstannane **20** and the known (*E*)-vinylboronic acid **21**,[21] respectively (Scheme 4). The Stille coupling of (*Z*)-vinyl bromide **19** with (*Z*)-vinyl stannane **20** under Corey's modified conditions [[$Pd(PPh_3)_4$], CuCl, LiCl, DMSO/THF (1:1), 60°C][10,22] provided 37,38-dihydrogambierol (**15**) in high yield. On the other hand, the Suzuki–Miyaura coupling[13] of **19** with (*E*)-vinylboronic acid **21** with a catalytic amount of [$Pd(PPh_3)_4$] and Na_2CO_3 in DME/H_2O (4:1) at 95°C furnished (32*E*)-37,38-dihydrogambierol (**16**) in excellent yield. The synthesis of analogue **17** is summarized in Scheme 5. Oxidation of **11** and Takai iodo-olefination ($CrCl_2$, CHI_3)[23] of the derived aldehyde gave (*E*)-vinyl iodide **22** together with its *Z* isomer in an acceptable selectivity (*E*:*Z* > 10:1 determined by ^1H NMR spectroscopy, 71% combined yield). Global desilylation of **22** followed by Stille coupling with (*Z*)-vinylstannane **23** under established conditions[10] delivered (32*E*)-gambierol (**17**) along with a small amount of its *Z* isomer, gambierol; these isomers were separated by HPLC. Truncated analogue **18** was prepared by the Stille coupling of **19** with tributyl(vinyl)tin (Scheme 4).

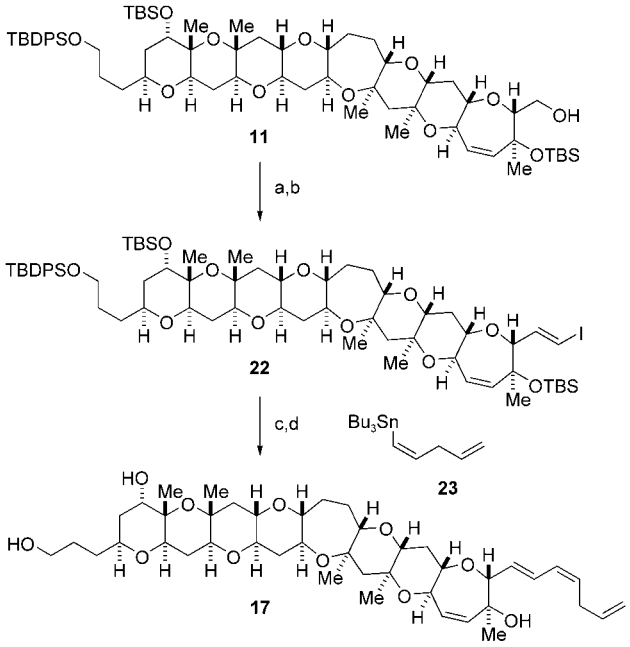
To evaluate the H-ring functionalities, analogues **24**–**26**, each of which has the triene side chain in the natural form, were designed and synthesized based on our total synthesis of **1**.[10] The synthesis of 28,29-dihydro-30-desmethylgambierol (**24**) commenced with compound **6** (Scheme 6). Reductive debenzylation of **6** by exposure to excess lithium di-*tert*-butylbiphenylide (LiDBB)[24] was followed by selective protection of the C1 hydroxy group to give *tert*-butyldiphenylsilyl (TBDPS) ether **27** in 79% yield for the two steps. Further silylation of the C6 hydroxy group and subsequent selective cleavage of the C32 primary TBS ether under acidic condi-



Scheme 3. Reagents and conditions: a) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (1:1), 0°C; b) $Br^-Ph_3P^+(CH_2)_5CH_3$, NaHMDS, THF, 0°C, 58% (two steps); c) HF·pyridine, THF, RT, 81%; d) H_2, 10% Pd/C, EtOAc, RT, 59%; e) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, RT; f) 5-(pentane-1-sulfonyl)-1-phenyl-1*H*-tetrazole **13**, KHMDS, THF, −78°C→RT, 70% (two steps); g) HF·pyridine, THF, RT, 87%; h) HPLC separation of configurational isomers (**9**: 58%; **10**: 29%). DMSO = dimethylsulfoxide; HPLC = high-performance liquid chromatography.



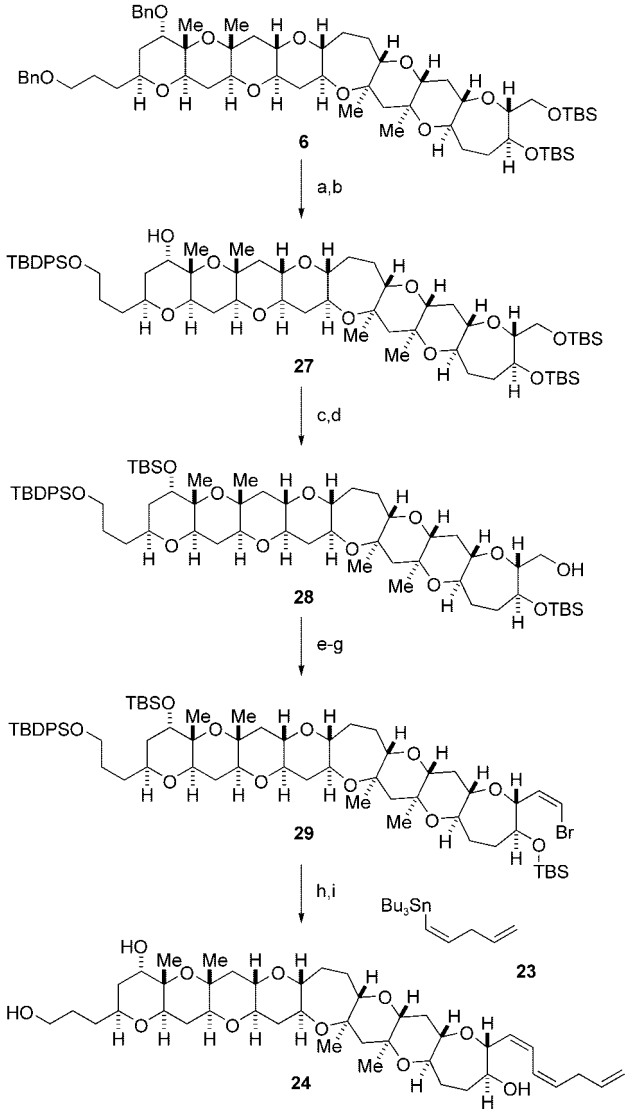
Scheme 4. Reagents and conditions: a) **20**, [Pd(PPh$_3$)$_4$], CuCl, LiCl, DMSO/THF (1:1), 60 °C, 91 %; b) **21**, [Pd(PPh$_3$)$_4$], Na$_2$CO$_3$, DME/H$_2$O (4:1), 95 °C, 91 %; c) tributyl(vinyl)tin, [Pd(PPh$_3$)$_4$], CuCl, LiCl, DMSO/THF, 60 °C, 26 % (45 % based on recovered **19**). DME = dimethoxyethane.



Scheme 5. Reagents and conditions: a) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, RT; b) $CrCl_2$, CHI_3, THF, RT→40 °C, 71 % (two steps); c) HF·pyridine, THF, RT, quantitative; d) **23**, [Pd(PPh$_3$)$_4$], CuCl, LiCl, DMSO/THF (1:1), RT, 84 %.

tions led to alcohol **28** in 80 % yield for the two steps. Oxidation of **28** with SO_3·pyridine and Corey–Fuchs olefination,[25] followed by stereoselective reduction of the derived dibromoolefin under conditions [nBu$_3$SnH, Pd(PPh$_3$)$_4$] reported by Uenishi and co-workers[26] afforded (*Z*)-vinyl bromide **29** in 47 % overall yield. Global deprotection of the silyl protective groups with HF·pyridine and the ensuing Stille coupling with (*Z*)-vinylstannane **23**[27] furnished analogue **24** in 63 % yield for the two steps. Two other analogues, 28,29-dihydrogambierol (**25**) and 30-desmethylgambierol (**26**), were prepared by using a similar chemistry to that described for the synthesis of **24**. 28,29-Dihydrogambierol (**25**) was accessible from alcohol **11** (Scheme 7). After reduction of the H-ring double bond of **11**, the derived alcohol **30** was elaborated to analogue **25** by the sequence described above. The synthesis of 30-desmethylgambierol (**26**) commenced with enone **31**,[10] which is derived from **2** in five steps as previously reported (Scheme 8). Reduction of the carbonyl group under Luche conditions[28] gave allylic alcohol **32** in 78 % yield after separation of a small amount of the undesired diastereomer by flash chromatography. Further protecting-group manipulations led to alcohol **33**, to which the triene side chain was incorporated by modified Stille coupling to afford analogue **26**.

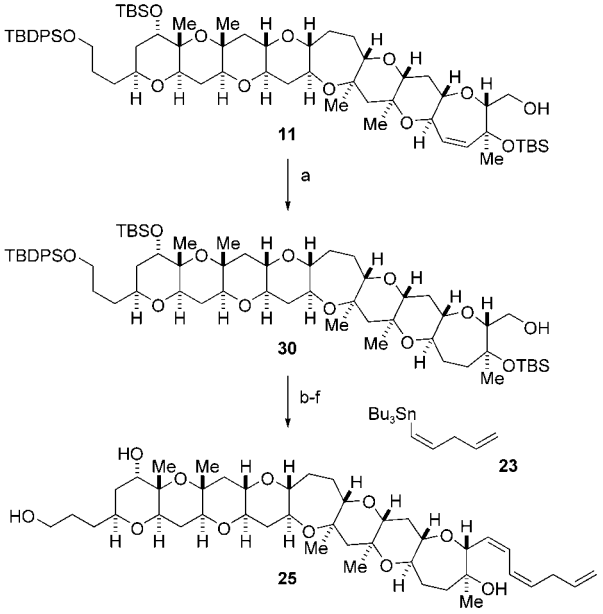
Synthesis of the left-wing modified analogues: With a series of right-wing modified analogues in hand, we next turned our attention to the modification of the C1 and C6 hydroxy groups. 6-*epi*-Gambierol (**34**) and 6-deoxygambierol (**35**) were targeted in order to evaluate the effect of the C6 hydroxy group on toxicity. Initially, the C6 axial-oriented hydroxy group of **36**[10] was inverted through an oxidation–reduction sequence (Scheme 9). Alcohol **36** was oxidized with TPAP in the presence of NMO and the resultant ketone was reduced stereoselectively with $NaBH_4$ (methanol/CH_2Cl_2, −78 °C) to give alcohol **37** (d.r. = 6.9:1) in good overall yield. As shown in Figure 1, the stereochemistry at the C6 position of **37** was unambiguously confirmed by ^{1}H NMR analysis of the corresponding acetate ($J_{5eq,6}$ = 5.5 Hz, $J_{5ax,6}$ = 10.8 Hz). Protection of **37** as the TBS ether gave tetra-silyl ether **38**, which was then elaborated to 6-*epi*-gambierol (**34**) following the same protocol as described for the synthesis of analogue **24**. On the other hand, for the synthesis of 6-deoxygambierol (**35**), alcohol **37** was treated with thiocarbonyldiimidazole to give the imidazolylthiocarbonyl derivative **40**. Reduction of **40** with nBu$_3$SnH in the presence of 2,2′-azobisisobutyronitrile (AIBN) produced deoxygenated



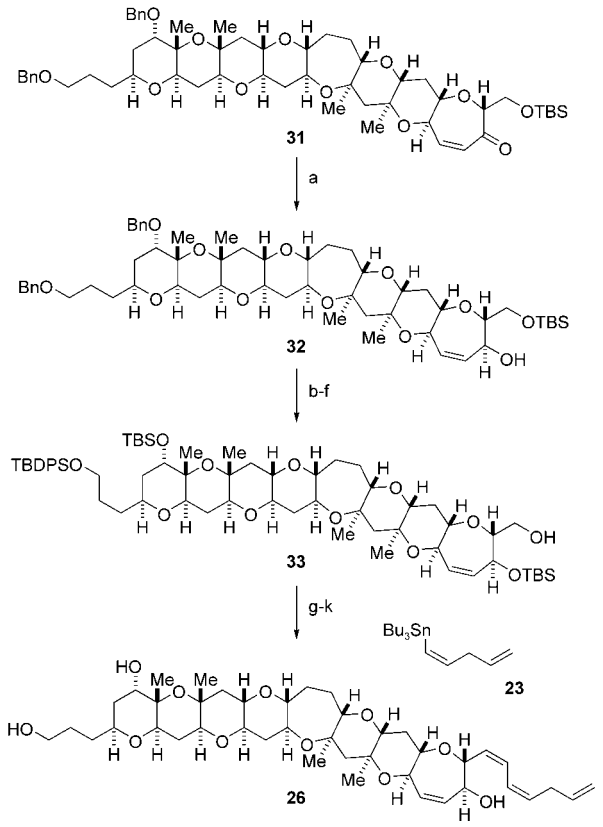
Scheme 6. Reagents and conditions: a) LiDBB, THF, −78→−40°C; b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, RT, 79% (two steps); c) TBSOTf, Et_3N, CH_2Cl_2, 0°C→RT; d) CSA, MeOH/CH_2Cl_2 (1:1), 0°C, 80% (two steps); e) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (1:1), 0°C; f) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0°C; g) $n$$Bu_3SnH$, $[Pd(PPh_3)_4]$, benzene, RT, 47% (three steps); h) HF·pyridine, THF, RT, 92%; i) **23**, $[Pd(PPh_3)_4]$, CuCl, LiCl, DMSO/THF (1:1), 60°C, 68%. LiDBB = lithium di-*tert*-butylbiphenylide; TBDPS = *tert*-butyldiphenylsilyl; DMAP = *N*,*N*-dimethylaminopyridine.

product **41**, which was converted into the 6-deoxy analogue **35** via **42** in a way similar to that described above.

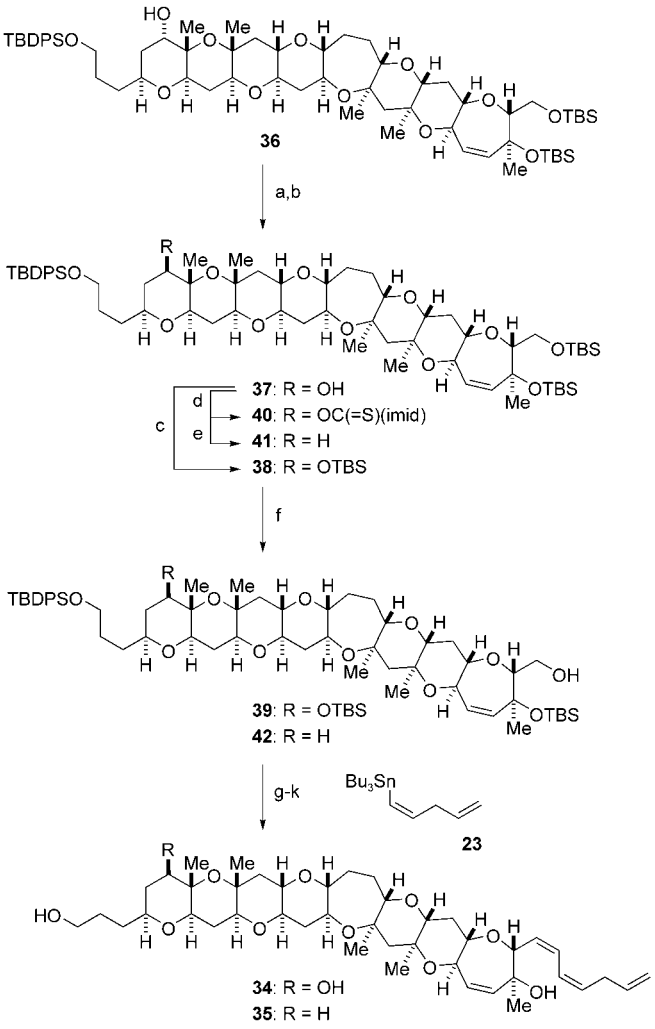
To investigate the role of the terminal C1 primary hydroxy group, we prepared 1-*O*-methylgambierol (**43**) and 1-deoxygambierol (**44**) (Scheme 10). The synthesis of 1-*O*-methylgambierol (**43**) commenced with (Z)-vinyl bromide **45**. During the course of our total synthesis of gambierol, we found that the three silyl protecting groups of **45** could be differentially removed by controlling the reaction time of the deprotection step. As expected, selective liberation of the C1 hydroxy group was realized by brief exposure of **45** to HF·pyridine; this reaction gives rise to alcohol **46** in 86% yield. Treatment of **46** with methyl trifluoromethanesulfonate in the presence of 2,6-di-*tert*-butylpyridine afforded



Scheme 7. Reagents and conditions: a) H_2, 10% Pd/C, EtOAc, room temperature, 95%; b) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (3:2), 0°C; c) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0°C; d) $n$$Bu_3SnH$, $[Pd(PPh_3)_4]$, benzene, RT, 74% (three steps); e) HF·pyridine, THF, RT, quantitative; f) **23**, $[Pd(PPh_3)_4]$, CuCl, LiCl, DMSO/THF (1:1), 60°C, 64%.



Scheme 8. Reagents and conditions: a) $NaBH_4$, $CeCl_3$·$7H_2O$, MeOH, 0°C, 78%; b) TBSOTf, Et_3N, CH_2Cl_2, 0°C→RT; c) LiDBB, THF, −78→−40°C, 74% (two steps); d) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, RT, 85%; e) TBSOTf, Et_3N, CH_2Cl_2, 0°C→RT; f) CSA, MeOH/CH_2Cl_2 (1:1), 0°C, 81% (two steps); g) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (1:1), 0°C; h) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0°C, 47% (two steps); i) $n$$Bu_3SnH$, $[Pd(PPh_3)_4]$, benzene, RT; j) HF·pyridine, THF, RT; k) **23**, $[Pd(PPh_3)_4]$, CuCl, LiCl, DMSO/THF (1:1), 60°C, 34% (three steps).



Scheme 9. Reagents and conditions: a) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, RT, 97%; b) $NaBH_4$, MeOH, −78°C, 83% + 12% of **36**; c) TBSOTf, Et_3N, CH_2Cl_2, 0°C→RT; d) $(Im)_2C{=}S$, DMAP, toluene, 110°C, 94%; e) $n$$Bu_3SnH$, AIBN, toluene, 110°C; f) CSA, MeOH/CH_2Cl_2 (1:1), 0°C, 86% (two steps) for **39**, 97% (two steps) for **42**; g) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, RT; h) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0°C; i) $n$$Bu_3SnH$, $[Pd(PPh_3)_4]$, benzene, RT; j) HF•pyridine, THF, RT; k) **23**, $[Pd(PPh_3)_4]$, CuCl, LiCl, DMSO/THF (1:1), 60°C, 51% (five steps) for **34**, 46% (five steps) for **35**. Im = imidazole; AIBN = 2,2′-azobisisobutyronitrile.

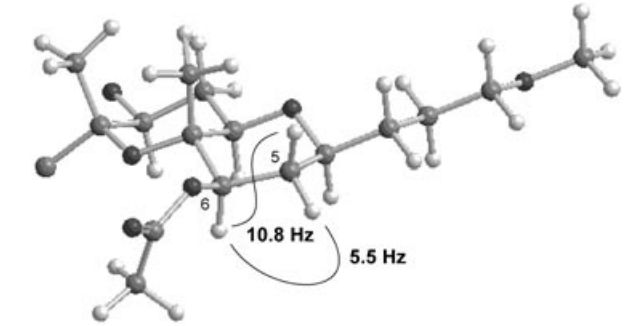
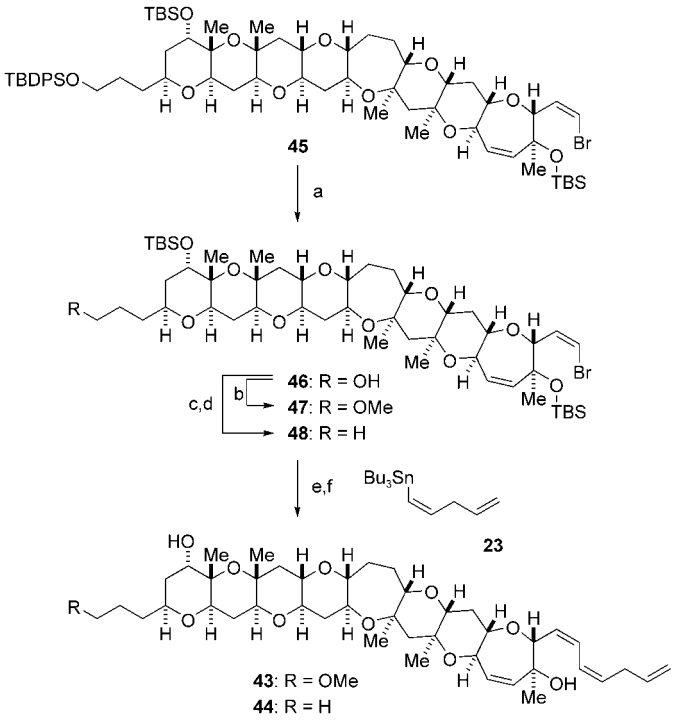


Figure 1. Confirmation of the stereochemistry at the C6 position by pertinent ^1H NMR coupling constants: $^3J_{5eq,6} = 5.5$ Hz, $^3J_{5ax,6} = 10.8$ Hz. The benzyl group was replaced with a methyl group for clarity.



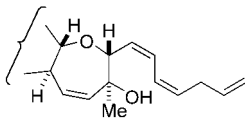
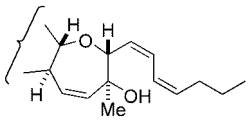
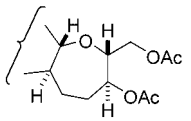
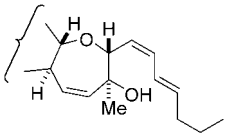
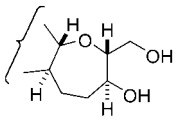
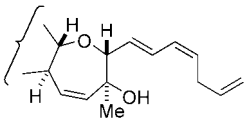
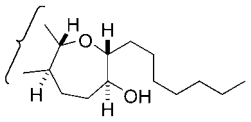
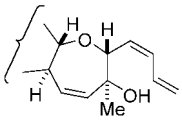
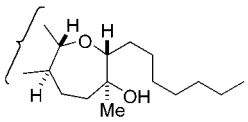
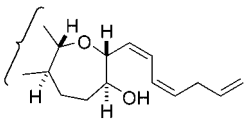
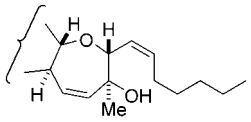
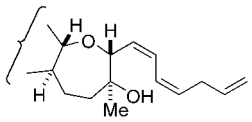
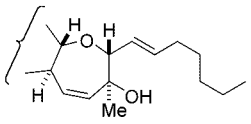
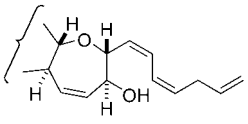
Scheme 10. Reagents and conditions: a) HF•pyridine, THF, RT, 86%; b) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, RT, 82%; c) MsCl, Et_3N, CH_2Cl_2, 0°C; d) $LiBHEt_3$, THF, 0°C→RT, 96% (two steps); e) HF•pyridine, THF, RT; f) **23**, $[Pd(PPh_3)_4]$, CuCl, LiCl, DMSO/THF (1:1), 60°C, 86% (two steps) for **43**, 82% (two steps) for **44**. Ms = methanesulfonyl.

methyl ether **47** in high yield without affecting the sensitive (*Z*)-vinyl bromide portion. Removal of the remaining silyl protecting groups and the ensuing modified Stille coupling with (*Z*)-vinylstannane **23** furnished 1-*O*-methyl analogue **43**. 1-Deoxygambierol (**44**) was also prepared from alcohol **46** by reduction of the corresponding mesylate. Thus, treatment of **46** with methanesulfonyl chloride in the presence of triethylamine gave the corresponding mesylate, which was reduced with $LiBHEt_3$ to afford the deoxygenated product **48** in excellent yield. Elaboration of **48** into the desired analogue **44** was readily accomplished as described for the synthesis of **43**.

Biological evaluation: The toxicities (MLD values) of synthetic gambierol (**1**) and its analogues against mice were next determined by intraperitoneal (ip) injection. The results are summarized in Tables 1 and 2. All toxic analogues except for compounds **43** and **44** caused death of the mice within 15–30 min of ip injection at the minimum lethal dose level indicated in Tables 1 and 2. In addition, at a lower dose level for all the active analogues, mice showed typical neurological symptoms, as observed in the case of gambierol.[29] On the other hand, such changes were not observed for the inactive compounds. For analogues **43** and **44**, death of the mice occurred 45–145 min after the ip injection.

Not surprisingly, simple analogues **3** and **4** were completely inactive, which clearly indicates that the octacyclic polyether core structure itself does not exert toxicity. Analogues **5** and **8**, both of which contain a heptyl chain in place of the

Table 1. Minimal lethal dose (MLD) values of gambierol (**1**) and right-wing modified analogues **3–5**, **8–10**, **15–18**, and **24–26** against mice.

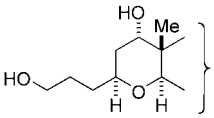
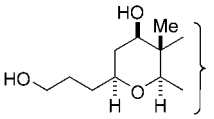
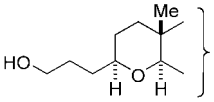
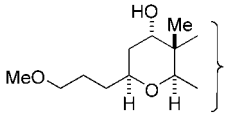
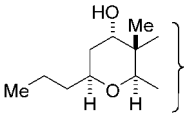
	Structure	MLD [mg kg^{-1}] (ip)	Relative activity		Structure	MLD [mg kg^{-1}] (ip)	Relative activity
1		0.050–0.075	1	**15**		0.065	1
3		>8.20 (inactive)	–	**16**		0.134	1/2
4		>18.3 (inactive)	–	**17**		0.336	1/5
5		>7.63 (inactive)	–	**18**		1.18	1/18
8		>12.9 (inactive)	–	**24**		>11.9 (inactive)	–
9		1.66	1/25	**25**		7.95	1/120
10		>12.9 (inactive)	–	**26**		0.340	1/5

natural triene side chain, showed no detectable toxicity, underlining the importance of the functionalities of the H ring as well as the double bond(s) within the side chain.

The importance of the conjugated diene system within the triene side chain was revealed by the evaluation of the toxicity of the analogues that contain the H-ring functionalities. 34,35,37,38-Tetrahydrogambierol (**9**) exhibited only moderate toxicity against mice (MLD 1.66 mg kg^{-1}, ca. 25-fold less active than **1**), and (32*E*)-34,35,37,38-tetrahydrogambierol (**10**), in which the configuration of the C32=C33 double bond is altered ($Z \rightarrow E$), showed no detectable toxicity. These results suggest that the conjugated diene system, which strongly restricts the orientation of the side chain, is an important and preferred structural feature for exhibiting potent activity. On the other hand, 37,38-dihydrogambierol (**15**) and (34*E*)-37,38-dihydrogambierol (**16**) were as potent as the parent **1**, which indicates that reduction of the C37=C38 double bond and inversion of the configuration of the C34=C35 double bond are irrelevant to toxicity. In addition to these compounds, we evaluated the toxicity of (32*E*)-gambierol (**17**) and the truncated analogue **18**. Interestingly, analogue **17** retained lethality about fivefold less active than that of the parent **1**. By comparing the structures of **10** and **17**, the conjugated diene system within the side chain again turns out to be important for exhibiting potent toxicity. In contrast, analogue **18**, which bears a butadiene side chain, was found to exhibit lower toxicity (MLD 1.18 mg kg^{-1}) than compounds **15–17**, which suggests that the length of the side chain in gambierol is also important for toxicity.

During the evaluation of analogues **24–26**, which possess the natural triene side chain, we found that the C28=C29 double bond within the H ring has a considerable effect on biological activity. To our surprise, 28,29-dihydro-30-desmethylgambierol (**24**) was completely inactive. 30-Desmethylgambierol (**26**) displayed toxicity about fivefold less active than **1** (MLD 0.34 mg kg^{-1}), whereas 28,29-dihydrogambierol (**25**) was approximately 120-fold less active (MLD 7.95 mg kg^{-1}). These results strongly indicate that the C28=C29 double bond is an indispensable structural element for exerting potent toxicity, whilst the C30 methyl group is not critical although it is possibly important. Reduction of the C28=C29 double bond should cause significant changes in

Table 2. Minimal lethal dose (MLD) values of gambierol (**1**) and left-wing modified analogues **34**, **35**, **43**, and **44** against mice.

	Structure	MLD [mg kg^{-1}]	Relative activity
1		0.050–0.075	1
34		0.065	1
35		0.19	1/3
43		0.42	1/6
44		0.20	1/3

the conformation of the H ring and consequently the orientation of the triene side chain. The drastic decrease in the toxicity of analogue **25** could be ascribed to the conformational change of the right-wing of the molecule. This was also supported by molecular mechanics calculations of compounds **1**, **25**, and **26**. A Monte Carlo conformational search with the MM3* forcefield implemented in Macromodel® version 8.0 was carried out for each compound simulated in water. Analogue **25**, in which the C28=C29 double bond is removed, adopts a conformation very different from that of **1**, whereas the conformation of analogue **26**, which lacks the C30 methyl group, is similar to that of parent **1** (Figure 2).

Finally, the role of the C1 and C6 hydroxy groups was established by analyzing analogues **34**, **35**, **43**, and **44** (Table 2). Since both 6-*epi*-gambierol (**34**) and 6-deoxygambierol (**35**) displayed activity comparable to that of parent **1**, it can be assumed that the C6 hydroxy group has essentially no influence on the biological activity of gambierol. 1-*O*-Methylgambierol (**43**) and 1-deoxygambierol (**44**) also retained potent neurotoxicity (MLD 0.42 and 0.20 mg kg^{-1}, respectively). However, these analogues required a longer time to cause death in mice (45–145 min after ip injection) than other active analogues, which suggests that these C1 modified analogues may have relatively low absorption and/or distribution properties. In any case, it can be concluded that the C1 and C6 hydroxy groups are not essential structural elements for exhibiting toxicity, though their presence is preferred.

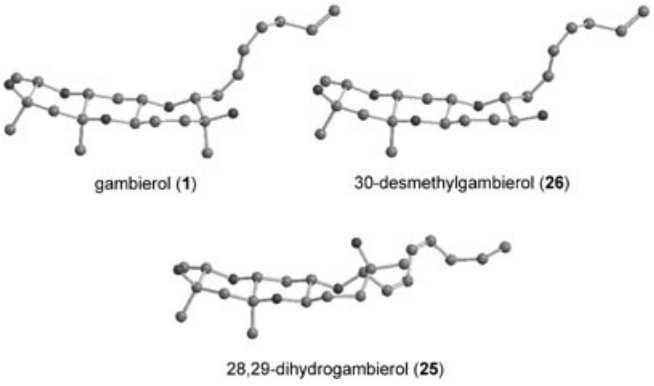


Figure 2. Lowest energy conformers for gambierol (**1**), 28,29-dihydrogambierol (**25**) and 30-desmethylgambierol (**26**). The A–E ring portion and hydrogen atoms have been removed for clarity.

Conclusion

By virtue of our practical synthetic route to gambierol, diverted total synthesis of gambierol analogues and systematic and detailed structure–activity relationship (SAR) studies of this complex marine toxin have been realized for the first time. The SAR study described herein has revealed that the structural elements of gambierol indispensable for exhibiting potent toxicity are the C28=C29 double bond, and the unsaturated side chain of specific length. In contrast to these important structural elements, the C1 and C6 hydroxy groups, the C30 axial-oriented methyl group, and the C34=C35 double bond are not essential but are preferred functional groups for exhibiting potent toxicity (Figure 3). The results presented here will allow the rational design of photoaffinity labeling and/or biotin-tagged probe molecules that will be useful for detailed biological studies on gambierol. Further studies along this line are currently underway and will be reported elsewhere.

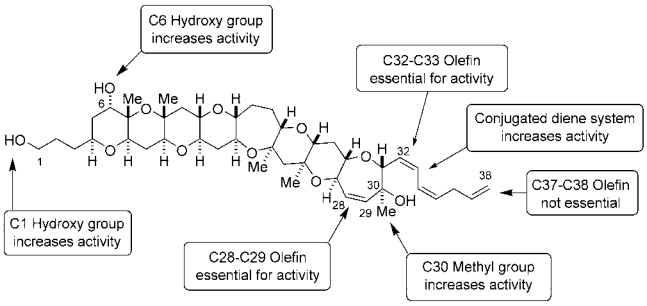


Figure 3. Summary of the structure-activity relationships of gambierol.

Experimental Section

General: All reactions sensitive to air and/or moisture were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with anhydrous solvents. All anhydrous solvents were purchased from Kanto Chemical Co. and used without further drying. Triethylamine was distilled from calcium hydride under an argon atmosphere. Tetrakis(triphenylphosphine)palladium(0) was prepared according to the literature protocol[30] and stored under an atmosphere of argon below −20 °C. Lithium chloride was dried by heating under a high vacuum prior to use. All other reagents purchased were of the highest commercial quality and used as received unless otherwise stated. Analytical thin-layer chromatography was carried out by using E. Merck silica gel 60 F254 plates (0.25 mm thickness). Flash chromatography was carried out with Fuji Silysia silica gel BW300 (200–400 mesh). Optical rotations were recorded on a JASCO DIP-350 digital polarimeter; specific optical rotations ($[\alpha]_D$)

are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra spectra were recorded on a JASCO FT/IR-420 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL A500 or Bruker DRX-500 spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard [^{1}H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), C_5HD_4N (8.50); ^{13}C NMR, $CDCl_3$ (77.0), C_6H_6 (128.0), C_5D_5N (135.5)], and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Low- and high-resolution mass spectra were recorded on a JEOL SX-102A mass spectrometer under fast atom bombardment (FAB) conditions using *m*-nitrobenzyl alcohol (NBA) as the matrix. Experimental procedures and characterization data for compounds **6**, **7**, **12**, **13**, **20**, **27**–**30**, **32**, **33**, **38**–**42**, **47** and **48** are included in the Supporting Information.

Analogue 3: $Pd(OH)_2$/C (20%, cat.) was added to a solution of octacyclic polyether **2** (14.8 mg, 0.0156 mmol) in ethyl acetate (2 mL). The resulting mixture was stirred at room temperature under hydrogen atmosphere for 2 days and then filtered through a plug of Celite. The filtrate was concentrated under reduced pressure to give diol **3** (11.4 mg, 94%) as an amorphous solid: $[\alpha]_D^{29} = -5.2$ ($c = 0.16$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3444$, 2947, 2875, 1739, 1650, 1458, 1382, 1239, 1089, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.98$ (ddd, $J = 5.2$, 3.1, 2.1 Hz, 1H), 4.11 (dd, $J = 11.6$, 6.4 Hz, 1H), 3.99 (dd, $J = 11.6$, 4.6 Hz, 1H), 3.80–3.72 (m, 3H), 3.69 (dd, $J = 2.8$, 2.8 Hz, 1H), 3.65–3.57 (m, 2H), 3.47–3.39 (m, 2H), 3.34 (dd, $J = 11.0$, 4.9 Hz, 1H), 3.20 (ddd, $J = 11.0$, 9.8, 4.9 Hz, 1H), 3.17–3.05 (m, 3H), 3.01 (dd, $J = 12.8$, 3.4 Hz, 1H), 2.58 (br, 1H), 2.23 (ddd, $J = 11.9$, 4.6, 4.3 Hz, 1H), 2.10–1.33 (m, 29H), 1.32 (s, 3H), 1.30 (s, 6H), 1.22 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 170.1, 84.8, 82.5, 81.3, 81.0, 80.0, 79.7, 79.1, 76.4, 75.9, 75.8, 75.2, 75.1, 73.9, 73.5, 73.0, 72.2, 72.0, 70.8, 65.0, 62.8, 53.9, 43.6, 37.4, 35.5, 32.4, 32.0, 29.2, 28.5, 27.2, 27.0, 24.8, 24.2, 21.3, 21.2, 20.8, 20.3, 18.2, 16.1 ppm; HRMS (FAB): m/z calcd for $C_{40}H_{62}O_{14}Na$ [M^++Na]: 789.4037; found: 789.4033.

Analogue 4: K_2CO_3 (7.0 mg, 0.051 mmol) was added to a solution of diacetate **3** (5.3 mg, 0.0068 mmol) in methanol (1 mL). The resulting mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 3→5→10% methanol/$CHCl_3$) to give analogue **4** (3.9 mg, 84%) as an amorphous solid: $[\alpha]_D^{29} = -3.3$ ($c = 0.11$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3435$, 2939, 2871, 1620, 1456, 1381, 1263, 1094, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$/CD_3OD): $\delta = 3.93$–3.85 (m, 3H), 3.85 (dd, $J = 2.8$, 2.8 Hz, 1H), 3.74–3.49 (m, 8H), 3.45–3.20 (m, 5H), 3.16 (dd, $J = 12.2$, 3.4 Hz, 1H), 2.32 (ddd, $J = 11.9$, 4.3, 4.3 Hz, 1H), 2.22–2.05 (m, 5H), 2.01–1.53 (m, 18H), 1.44 (m, 3H), 1.43 (m, 3H), 1.41 (m, 3H), 1.34 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD): $\delta = 87.8$, 85.6, 83.0, 82.5, 80.8, 80.6, 79.8, 77.2, 76.8, 76.6, 75.8, 75.5, 74.9, 74.5, 73.04, 72.97, 71.5, 71.0, 64.7, 62.6, 54.5, 43.9, 38.0, 36.6, 32.6 (×2), 29.6, 29.3, 29.1, 27.7, 27.3, 24.8, 21.8, 20.9, 18.7, 16.5 ppm; HRMS (FAB): m/z calcd for $C_{36}H_{58}O_{12}Na$ [M^++Na]: 705.3826; found: 705.3815.

Analogue 5: HF·pyridine (0.30 mL) was added to a solution of olefin **7** (8.7 mg, 0.0083 mmol) in THF (1 mL). The resulting mixture was stirred at room temperature for 2 days and then poured into cold saturated aqueous $NaHCO_3$ and stirred at room temperature for 1 h. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30:40 ethyl acetate/hexanes) to give an alcohol (5.6 mg, 72%) as a colorless oil: $[\alpha]_D^{29} = +22.9$ ($c = 0.042$ in benzene); IR (film): $\tilde{\nu}_{max} = 3441$, 2920, 1646, 1550, 1382, 1086 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): $\delta = 7.41$–7.40 (m, 2H),7.31–7.28 (m, 2H), 7.23–7.07 (m, 6H), 5.49–5.40 (m, 2H), 4.98 (d, $J = 12.2$ Hz, 1H), 4.55 (d, $J = 12.2$ Hz, 1H), 4.35 (dd, $J = 7.6$, 4.3 Hz, 1H), 4.31 (s, 2H), 4.10 (dd, $J = 12.2$, 4.0 Hz, H), 3.87 (ddd, $J = 14.6$, 7.3, 4.3 Hz, 1H), 3.58–3.54 (m, 3H), 3.40–3.30 (m, 4H), 3.26 (dd, $J = 12.2$, 3.4 Hz, 1H), 3.13 (ddd, $J = 11.3$, 9.2, 4.9 Hz, 1H), 3.06–2.97 (m, 3H), 2.40 (ddd, $J = 11.9$, 4.3, 4.3 Hz, 1H), 2.34 (dd, $J = 11.6$, 4.9 Hz, 1H), 2.22–1.93 (m, 10H), 1.87–1.44 (m, 14H), 1.34–1.04 (m, 7H), 1.32 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 0.87 ppm (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 140.4$, 139.5, 132.5, 130.4, 128.5, 128.3, 127.5, 85.1, 82.7, 81.9, 80.4, 80.3, 79.8, 79.5, 79.3, 77.8, 77.0, 76.1, 75.4, 74.9, 74.8, 74.7, 74.3, 74.1, 72.9, 72.7, 72.0, 70.5, 54.7, 44.7, 38.6, 37.0, 33.1, 33.0, 31.7, 29.5, 29.1, 28.5, 28.1, 27.9, 27.4, 26.4, 24.8, 22.9, 22.0, 21.6, 18.3, 16.3, 14.2 ppm; HRMS (FAB): m/z calcd for $C_{56}H_{80}O_{11}Na$ [M^++Na]: 951.5598; found: 951.5646.

$Pd(OH)_2$/C (cat.) was added to a solution of the above alcohol in ethyl acetate/methanol (1:1, v/v, 2 mL). The resulting mixture was stirred at room temperature under a hydrogen atmosphere for 2 days, and then filtered through a plug of Celite. The filtrate was concentrated under reduced pressure to give analogue **5** (4.5 mg, quantitative) as an amorphous solid: $[\alpha]_D^{29} = -4.6$ ($c = 0.15$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3437$, 2931, 2872, 1631, 1460, 1386, 1292, 1089, 1052, 755 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 3.79$ (dd, $J = 12.2$, 3.7 Hz, 1H), 3.76–3.71 (m, 1H), 3.66–3.62 (m, 2H), 3.52–3.48 (m, 3H), 3.41–3.06 (m, 8H), 3.02 (dd, $J = 12.5$, 3.4 Hz, 1H), 2.16 (ddd, $J = 11.6$, 4.3, 4.3 Hz, 1H), 2.01–1.93 (m, 4H), 1.89–1.42 (m, 21H), 1.37–1.18 (m, 10H), 1.31 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 0.87 ppm (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 87.7$, 86.1, 82.9, 81.3, 81.1, 80.3, 77.8, 77.2, 77.1, 76.2, 75.8, 75.5, 75.4, 75.1, 73.7, 73.4, 72.1, 62.9, 55.1, 49.6, 44.3, 38.7, 37.4, 36.2, 33.2, 33.1, 33.0, 30.5, 30.4, 29.9, 29.7, 29.6, 28.2, 27.8, 27.2, 25.3, 23.7, 21.9, 21.1, 18.8, 16.6, 14.4 ppm; HRMS (FAB): m/z calcd for $C_{42}H_{70}O_{11}Na$ [M^++Na]: 773.4816; found: 773.4803.

34,35,37,38-Tetrahydrogambierol (9): HF·pyridine (0.2 mL) was added to a solution of olefin **12** (8.5 mg, 0.0069 mmol) in THF (0.6 mL) cooled to 0°C. The resulting mixture was stirred at room temperature for 3 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ 3→5% methanol/$CHCl_3$) to give **9** (4.3 mg, 81%) as an amorphous solid: $[\alpha]_D^{30} = +10.6$ ($c = 0.12$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3439$, 2928, 2871, 1620, 1459, 1381, 1077, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.76$ (dd, $J = 12.8$, 2.8 Hz, 1H), 5.71 (ddd, $J = 11.0$, 7.6, 7.3 Hz, 1H), 5.48 (dd, $J = 12.8$, 1.8 Hz, 1H), 5.41 (dd, $J = 11.0$, 9.5 Hz, 1H), 4.22–4.20 (m, 2H), 3.79–3.76 (m, 2H), 3.70 (m, 1H), 3.64–3.59 (m, 2H), 3.45(m, 1H), 3.39–3.32 (m, 5H), 3.17–3.02 (m, 5H), 2.58 (m, 1H), 2.23 (ddd, $J = 11.9$, 4.3, 4.3 Hz, 1H), 2.18–1.82 (m, 10H), 1.77–1.45 (m, 11H), 1.40–1.22(m, 5H), 1.32 (s, 3H), 1.30 (s, 6H), 1.28 (s, 3H), 1.22 (s, 3H), 0.87 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 137.9$, 136.4, 130.8, 125.7, 84.8, 82.4, 82.2, 81.3, 79.9, 79.5, 79.1, 77.2, 76.3, 75.9, 75.8, 75.2, 75.1, 73.9, 72.2, 71.9, 71.8, 70.8, 62.8, 53.7, 43.6, 37.4, 35.5, 32.4, 32.1, 31.4, 29.2, 29.1, 28.6, 28.4, 27.0, 24.2, 22.5, 21.6, 21.3, 20.3, 18.2, 15.6, 14.0 ppm; HRMS (FAB): m/z calcd for $C_{43}H_{68}O_{11}Na$ [M^++Na]: 783.4659; found: 783.4670.

Perhydrogambierol (8): Pd/C (10%, cat.) was added to a solution of **9** (2.6 mg, 0.0034 mmol) in ethyl acetate (1 mL). The resulting mixture was stirred at room temperature under a hydrogen atmosphere overnight and then filtered through a plug of Celite. The filtrate was concentrated under reduced pressure to give perhydrogambierol (**8**) (1.5 mg, 59%) as an amorphous solid: $[\alpha]_D^{30} = -15.2$ ($c = 0.046$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3441$, 2927, 2872, 1650, 1460, 1382, 1087, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.78$–3.76 (m, 3H), 3.70 (m, 1H), 3.64–3.59 (m, 2H), 3.45 (ddd, $J = 13.7$, 4.9, 4.9 Hz, 1H), 3.38–3.34 (m, 2H), 3.21–3.02 (m, 7H), 2.23 (ddd, $J = 11.6$, 4.0, 4.0 Hz, 1H), 2.12–2.09 (m, 2H), 2.02–1.22 (m, 32H), 1.32 (s, 3H), 1.31 (s, 6H), 1.22 (s, 3H), 1.12 (s, 3H), 0.86 ppm (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 89.1$, 84.9, 84.3, 82.4, 80.4, 79.9, 79.1, 76.4, 75.9, 75.8, 75.2, 75.1 (×2), 74.9, 73.9, 72.4, 72.2, 70.8, 62.8, 53.9, 43.6, 40.0, 37.3, 35.5, 32.4, 32.0, 31.8, 30.5, 29.6, 29.3, 29.2, 28.5, 27.7, 26.9 (×2), 24.5, 24.2, 22.7, 21.3, 20.3, 18.3, 16.2, 14.1 ppm; HRMS (FAB): m/z calcd for $C_{43}H_{72}O_{11}Na$ [M^++Na]: 787.4972; found: 787.5000.

(32*E*)-34,35,37,38-Tetrahydrogambierol (10): *N*-Methylmorpholine *N*-oxide (11.3 mg, 0.0962 mmol), tetra-*n*-propylammonium perruthenate (cat.), and 4 Å molecular sieves were added to a solution of alcohol **11** (7.3 mg, 0.0063 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at room temperature for 20 min and then filtered through a plug of silica gel (eluted with ethyl acetate). The eluent was concentrated under reduced pressure to give a crude aldehyde, which was immediately used in the next reaction.

KHMDS (0.5 M in toluene, 0.065 mL, 0.065 mmol) was added to a solution of 5-(pentane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**13**) (20.6 mg, 0.07 mmol) in THF (0.5 mL) cooled to −78°C . The resulting solution was stirred at −78°C for 40 min, and a solution of the above aldehyde in THF (0.5 mL + 1.2 mL rinse) was added. The resultant mixture was stir-

red at −78 °C for 1 h and then allowed to warm to room temperature. This mixture was stirred at room temperature overnight and then quenched with water. The solution was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 8→10→20% ether/hexanes) to give olefin **14** as an inseparable 2:1 mixture of isomers (5.4 mg, 70% for the two steps) as a colorless oil.

HF·pyridine (0.1 mL) was added to a solution of the above mixture of isomers **14** (5.4 mg, 0.0044 mmol) in THF (0.3 mL) cooled to 0 °C. The resulting mixture was stirred at room temperature for 4 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel and eluted with 5% methanol/$CHCl_3$. Further purification by HPLC (Asahi-pack ODP-60, 50% CH_3CN/H_2O) gave **10** (0.98 mg, 29%) and (*Z*)-olefin analogue **9** (1.9 mg, 58%) as amorphous solids. **10**: $[\alpha]_D^{30} = -17.7$ ($c = 0.033$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3437$, 2927, 2872, 1623, 1463, 1383, 1086, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.75$ (m, 1H), 5.74 (dd, $J =$ 12.9, 2.7 Hz, 1H), 5.47 (dd, $J = 15.6$, 7.1 Hz, 1H), 5.47 (dd, $J = 12.9$, 2.0 Hz, 1H), 4.20 (ddd, $J = 9.4$, 2.7, 2.0 Hz, 1H), 3.85 (d, $J = 7.1$ Hz, 1H), 3.79–3.76 (m, 2H), 3.70 (m, 1H), 3.66–3.58 (m, 2H), 3.45 (ddd, $J = 10.5$, 4.9, 4.9 Hz, 1H), 3.36–3.31 (m, 2H), 3.17–3.03 (m, 4H), 3.02 (dd, $J = 12.9$, 3.6 Hz, 1H), 2.24 (m, 1H), 2.13–1.83 (m, 9H), 1.76–1.47 (m, 10H), 1.38–1.25 (m, 8H), 1.32 (s, 3H), 1.31 (s, 1H), 1.23 (s, 3H), 1.22 (s, 3H), 0.86 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 137.8$, 136.3, 130.7, 126.1, 87.5, 84.7, 82.4, 81.2, 79.9, 79.4, 79.1, 76.3, 75.9, 75.8, 75.3, 75.2, 75.1, 73.9, 72.2, 71.9, 71.8, 70.8, 62.8, 53.7, 43.6, 37.3, 35.5, 32.5, 32.4, 32.0, 31.4, 29.2, 28.7, 28.5, 26.9, 24.2, 22.5, 21.7, 21.3, 20.3, 18.2, 15.6, 14.0 ppm; HRMS (FAB): *m/z* calcd for $C_{43}H_{68}O_{11}Na$ [M^++Na]: 783.4659; found: 783.4680.

37,38-Dihydrogambierol (15): CuCl (39.6 mg, 0.400 mmol), LiCl (20.2 mg, 0.477 mmol), and $[Pd(PPh_3)_4]$ (3.2 mg, 0.0028 mmol) were added to a solution of (*Z*)-vinyl bromide **19** (4.7 mg, 0.0061 mmol) and (*Z*)-vinylstannane **20** (71.5 mg, 0.199 mmol) in degassed DMSO/THF (1:1, v/v, 2 mL). The resulting mixture was stirred at 60 °C for 2.5 days and then quenched with 5% NH_4OH. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 3→5% methanol/$CHCl_3$) to give **15** (4.2 mg, 91%) as an amorphous solid: $[\alpha]_D^{30} = -8.0$ ($c = 0.11$ in methanol); IR (film): $\tilde{\nu}_{max} = 3437$, 2925, 2872, 1622, 1461, 1383, 1059 cm^{-1}; ^1H NMR (500 MHz, CD_3CN): $\delta = 6.46$ (dd, $J = 11.6$, 11.4 Hz, 1H), 6.32 (ddd, $J = 11.6$, 10.7, 1.1 Hz, 1H), 5.70 (dd, $J = 12.9$, 2.7 Hz, 1H), 5.56 (m, 1H), 5.42 (m, 1H), 5.39 (dd, $J = 12.9$, 1.9 Hz, 1H), 4.31 (d, $J = 8.9$ Hz, 1H), 4.21 (ddd, $J = 9.4$, 2.7, 1.9 Hz, 1H), 3.75 (dd, $J = 11.5$, 4.4 Hz, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 3.55–3.38 (m, 4H), 3.34 (m, 1H), 3.23–3.13 (m, 3H), 3.07–3.00 (m, 2H), 2.83 (d, $J = 1.9$ Hz, 1H), 2.61 (s, 1H), 2.53 (t, $J = 5.4$ Hz, 1H), 2.19–2.08 (m, 3H), 1.97–1.69 (m, 8H), 1.65–1.38 (m, 13H), 1.30 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 0.90 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta = 140.6$, 135.0, 131.1, 128.5, 127.9, 125.3, 85.6, 83.1, 82.9, 82.0, 80.4, 80.2, 79.8, 77.1, 76.8, 76.7, 76.5, 75.9, 75.5, 74.6, 73.1, 72.7 (×2), 71.7, 62.5, 54.8, 44.1, 38.2, 36.6, 32.9 (×2), 30.0, 29.7, 29.3, 27.9, 25.0, 23.5, 21.7, 21.4, 20.8, 18.7, 15.9, 14.0 ppm; HRMS (FAB): *m/z* calcd for $C_{43}H_{66}O_{11}Na$ [M^++Na]: 781.4503; found: 781.4529.

(34*E*)-37,38-Dihydrogambierol (16): Na_2CO_3 (2.2 mg, 0.0133 mmol), (*E*)-vinylboronic acid **21** (12.8 mg, 0.112 mmol), and $[Pd(PPh_3)_4]$ (5.2 mg, 0.0045 mmol) were added to a solution of (*Z*)-vinyl bromide **19** (5.0 mg, 0.0065 mmol) in DME/water (4:1, v/v, 1 mL). After being stirred at 95 °C for 4.5 h, the reaction mixture was diluted with $CHCl_3$ and washed with brine. The aqueous layer was separated and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 2% methanol/$CHCl_3$) to give analogue **16** (4.5 mg, 91%) as an amorphous solid: $[\alpha]_D^{30} = +17.0$ ($c = 0.155$ in methanol); IR (film): $\tilde{\nu}_{max} = 3436$, 2951, 2874, 1635, 1460, 1381, 1123, 1073 cm^{-1}; ^1H NMR (500 MHz, CD_3CN): $\delta = 6.39$ (ddd, $J = 15.1$, 11.1, 1.1 Hz, 1H), 6.11 (dd, $J = 11.1$, 11.1 Hz, 1H), 5.74 (m, 1H), 5.70 (dd, $J =$ 12.9, 2.7 Hz, 1H), 5.39 (dd, $J = 12.9$, 1.9 Hz, 1H), 5.28 (dd, $J = 11.1$, 8.4 Hz, 1H), 4.29 (d, $J = 8.4$ Hz, 1H), 4.21 (ddd, $J = 9.5$, 2.7, 1.9 Hz, 1H), 3.75 (dd, $J = 11.5$, 4.4 Hz, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 3.51 (ddd, $J =$ 10.6, 8.9, 5.0 Hz, 1H), 3.46–3.41 (m, 3H), 3.35 (m, 1H), 3.23–3.13 (m, 3H), 3.07–3.01 (m, 2H), 2.84 (d, $J = 1.8$ Hz, 1H), 2.61 (s, 1H), 2.56 (t, $J =$ 5.4 Hz, 1H), 2.11–2.06 (m, 3H), 1.96–1.69 (m, 8H), 1.65–1.37 (m, 13H), 1.30 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.202 (s, 3H), 1.198 (s, 3H), 0.89 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta = 139.6$, 136.9, 132.2, 130.0, 126.5, 125.5, 84.5, 82.4, 81.9, 80.9, 79.4, 79.2, 78.7, 76.0, 75.8, 75.7, 75.4, 74.8, 74.4, 73.5, 72.1, 71.7 (×2), 70.7, 61.5, 53.7, 43.1, 37.2, 35.6, 34.5, 31.9, 31.8, 28.7, 28.3, 26.9, 24.0, 22.1, 20.7, 20.3, 19.8, 17.6, 14.9, 13.0 ppm; HRMS (FAB): *m/z* calcd for $C_{43}H_{66}O_{11}Na$ [M^++Na]: 781.4503; found: 781.4520.

(*E*)-Vinyl iodide 22: *N*-Methylmorpholine *N*-oxide (10.2 mg, 0.0868 mmol), a catalytic amount of tetra-*n*-propylammonium perruthenate, and 4 Å molecular sieves (ca. 10 mg) were added to a solution of alcohol **11** (10.5 mg, 0.0091 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at room temperature for 40 min and then filtered through a plug of silica gel and eluted with ethyl acetate. The eluent was concentrated under reduced pressure to give a crude aldehyde, which was immediately used in the next reaction.

A solution of the above aldehyde and iodoform (11.4 mg, 0.0290 mmol) in THF (0.5 mL + 1 mL rinse) was added by cannula to a suspension of $CrCl_2$ (11.0 mg, 0.0895 mmol) in THF (0.5 mL). After stirring the mixture at room temperature for 5 h, further $CrCl_2$ (11.0 mg, 0.0895 mmol) and iodoform (11.0 mg, 0.0279 mmol) were added. The resulting mixture was stirred at room temperature for a further 4 h 40 min and then allowed to warm to 40 °C. The reaction mixture was stirred at this temperature for 75 min and then poured into water and extracted several times with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 5→10% ethyl acetate/hexanes) to give (*E*)-vinyl iodide **22** (8.3 mg, 71%) as a colorless oil: ^1H NMR (500 MHz, C_6D_6): $\delta = 7.79$–7.77 (m, 4H), 7.24–7.23 (m, 6H), 6.91 (dd, $J = 14.5$, 4.0 Hz, 1H), 6.47 (dd, $J = 14.5$, 1.7 Hz, 1H), 5.74 (dd, $J = 13.0$, 2.5 Hz, 1H), 5.67 (dd, $J = 13.0$, 1.5 Hz, 1H), 4.22 (d, $J = 9.4$ Hz, 1H), 4.01 (dd, $J = 12.2$, 3.7 Hz, 1H), 3.89 (m, 1H), 3.86 (dd, $J = 4.0$, 1.7 Hz, 1H), 3.72–3.65 (m, 3H), 3.38–3.34 (m, 2H), 3.28 (dd, $J = 11.9$, 3.1 Hz, 1H), 3.18–3.08 (m, 3H), 3.03 (ddd, $J = 11.2$, 8.2, 2.9 Hz, 1H), 2.98 (dd, $J = 12.7$, 3.5 Hz, 1H), 2.44 (ddd, $J = 11.9$, 4.3, 3.9 Hz, 1H), 2.32 (dd, $J = 11.6$, 4.5 Hz, 1H), 2.14 (ddd, $J = 7.9$, 3.7, 3.7 Hz, 1H), 2.10–1.41 (m, 17H), 1.32 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.17 (s, 9H), 1.13 (s, 3H), 1.10 (s, 3H), 1.01 (s, 9H), 0.93 (s, 9H), 0.16 (s, 3H), 0.074 (s, 3H), 0.066 (s, 3H), 0.056 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 143.9$, 139.0, 136.0, 134.4, 130.7, 129.9, 128.5, 128.3, 88.3, 85.3, 82.9, 81.9, 80.2, 79.9, 79.7, 79.0, 77.1, 76.1, 76.0, 74.8, 74.1, 72.7, 72.4, 72.2, 72.1, 64.3, 54.4, 44.4, 39.2, 38.1, 32.4, 32.3, 29.2, 28.9, 27.9, 27.1, 26.2, 25.9, 24.7, 22.1, 21.9, 21.5, 19.5, 18.4, 18.3 (×2), 15.7, −1.9, −2.2, −4.0, −4.9 ppm.

(32*E*)-Gambierol (17): HF·pyridine (0.1 mL) was added to a solution of (*E*)-vinyl iodide **22** (8.3 mg, 0.0065 mmol) in THF (0.3 mL) cooled to 0 °C. The resulting mixture was stirred at room temperature for 4 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 3→5% methanol/$CHCl_3$) to give a triol (5.7 mg, quantitative) as an amorphous solid: $[\alpha]_D^{30} = -190.8$ ($c = 0.015$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3434$, 2947, 2874, 1609, 1458, 1382, 1085, 1049, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.66$ (dd, $J = 14.5$, 4.9 Hz, 1H), 6.41 (dd, $J =$ 14.5, 1.5 Hz, 1H), 5.67 (dd, $J = 12.9$, 2.6 Hz, 1H), 5.47 (dd, $J = 12.9$, 1.7 Hz, 1H), 4.16 (d, $J = 9.4$ Hz, 1H), 3.99 (dd, $J = 4.9$, 1.5 Hz, 1H), 3.84–3.75 (m, 2H), 3.70 (m, 1H), 3.64–3.58 (m, 2H), 3.45 (ddd, $J = 10.5$, 8.8, 5.1 Hz, 1H), 3.35–3.28 (m, 2H), 3.17–3.03 (m, 4H), 3.01 (dd, $J = 12.8$, 3.6 Hz, 1H), 2.59 (s, 1H), 2.23 (ddd, $J = 11.7$, 4.4, 4.0 Hz, 1H), 2.11–1.97 (m, 6H), 1.94–1.81 (m, 2H), 1.76–1.41 (m, 16H), 1.32 (s, 3H), 1.30 (s, 6H), 1.22 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 142.5$, 137.9, 131.1, 128.6, 87.9, 84.7, 82.4, 81.4, 79.8, 79.2, 79.1, 76.3, 75.82, 75.77, 75.6, 75.2, 75.1, 73.9, 72.2, 72.0, 71.5, 70.7, 62.8, 53.6, 43.5, 37.3, 35.5, 32.4, 31.8, 29.2, 28.5, 26.9, 24.1, 21.5, 21.3, 20.3, 18.2, 15.6 ppm; HRMS (FAB): *m/z* calcd for $C_{38}H_{57}IO_{11}Na$ [M^++Na]: 839.2843; found: 839.2808.

CuCl (34.7 mg, 0.351 mmol), LiCl (20.2 mg, 0.470 mmol), and $[Pd(PPh_3)_4]$ (3.4 mg, 0.0029 mmol) were added to a solution of the above triol

(4.7 mg, 0.0058 mmol) and (*Z*)-vinylstannane **23** (20.2 mg, 0.0564 mmol) in degassed DMSO/THF (1:1, v/v, 0.5 mL). The resulting mixture was stirred at room temperature overnight and then quenched with 5% NH_4OH. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 5% methanol/$CHCl_3$) to give **17** (3.7 mg, 84%) as an amorphous solid: $[\alpha]_D^{30} = -62.5$ ($c = 0.10$ in methanol); IR (film): $\tilde{\nu}_{max} = 3435, 2930, 2871, 1630, 1445, 1382, 1058\ cm^{-1}$; ^1H NMR (500 MHz, CD_3CN): $\delta = 6.59$ (dd, $J = 15.3, 11.2$ Hz, 1H), 6.08 (dd, $J = 11.2, 10.8$ Hz, 1H), 5.84 (dddd, $J = 17.2, 10.2, 6.3, 6.3$ Hz, 1H), 5.79 (dd, $J = 15.3, 5.2$ Hz, 1H), 5.69 (dd, $J = 12.9, 2.7$ Hz, 1H), 5.44 (ddd, $J = 10.8, 7.7, 7.7$ Hz, 1H), 5.38 (dd, $J = 12.9, 1.8$ Hz, 1H), 5.05 (dd, $J = 17.2, 1.8$ Hz, 1H), 4.98 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.21 (ddd, $J = 9.4, 2.7, 1.8$ Hz, 1H), 3.97 (d, $J = 5.2$ Hz, 1H), 3.75 (dd, $J = 11.4, 4.5$ Hz, 1H), 3.67 (m, 1H), 3.59–3.34 (m, 6H), 3.23–3.13 (m, 3H), 3.06–3.01 (m, 2H), 2.95–2.91 (m, 3H), 2.84 (m, 1H), 2.56 (m, 1H), 2.12 (m, 1H), 1.98–1.71 (m, 8H), 1.67–1.41 (m, 11H), 1.30 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 1.12 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta = 140.7, 137.7, 132.2, 131.0, 130.0, 129.6, 127.9, 115.4, 87.2, 85.5, 82.9, 82.0, 80.4, 80.2, 79.7, 77.0, 76.8, 76.7, 76.2, 75.8, 75.4, 74.5, 73.1, 72.7 (\times 2), 71.7, 62.5, 54.7, 44.1, 38.2, 36.6, 32.8 (\times 2), 32.5, 29.7, 29.3, 27.9, 25.0, 21.7, 21.5, 20.8, 18.6, 15.9$ ppm; HRMS (FAB): *m/z* calcd for $C_{43}H_{64}O_{11}Na$ [M^++Na]: 779.4346; found: 779.4326.

Analogue 18: CuCl (8.6 mg, 0.087 mmol), LiCl (4.5 mg, 0.11 mmol), and $[Pd(PPh_3)_4]$ (0.8 mg, 0.0007 mmol) were added to a solution of (*Z*)-vinyl bromide **19** (1.1 mg, 0.0014 mmol) and tributyl(vinyl)tin (0.015 mL, 0.050 mmol) in degassed DMSO/THF (1:1, v/v, 1 mL). The resulting mixture was stirred at 60°C for 2 days. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, and treated with 3% NH_4OH. The resulting mixture was stirred at room temperature for 10 min. The aqueous layer was extracted with $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3 \rightarrow 2\%$ methanol/$CHCl_3$) and then HPLC (Asahi-pack ODP-50, 45% CH_3CN/H_2O) to give diene **18** (0.27 mg, 26%) and **19** (0.45 mg). **18**: $[\alpha]_D^{24} = +96.3$ ($c = 0.02$ in $CHCl_3$); ^1H NMR (600 MHz, C_5D_5N): $\delta = 7.14$ (m, 1H), 6.48 (s, 1H), 6.34 (dd, $J = 11.4, 11.4$ Hz, 1H), 6.27 (d, $J = 12.6$ Hz, 1H), 6.05–5.94 (m, 2H), 5.85 (d, $J = 12.6$ Hz, 1H), 5.27 (d, $J = 16.8$ Hz, 1H), 5.18 (d, $J = 9.6$ Hz, 1H), 5.13 (brs, 1H), 4.83 (d, $J = 7.2$ Hz, 1H), 4.58 (brd, $J = 9.0$ Hz, 1H), 4.22 (brd, $J = 10.8$ Hz, 1H), 4.16 (m, 1H), 3.96 (brs, 1H), 3.92–3.86 (m, 2H), 3.73 (m, 1H), 3.64 (m, 1H), 3.59 (m, 1H), 3.46 (brd, $J = 11.4$ Hz, 1H), 3.34–3.22 (m, 4H), 2.46 (m, 1H), 2.25 (m, 1H), 2.18–2.02 (m, 6H), 2.02–1.66 (m, 11H), 1.63 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR (125 MHz, C_5D_5N): $\delta = 141.5, 134.3, 132.4, 130.6, 130.1, 118.6, 85.1, 84.0, 82.7, 81.8, 80.0, 79.9, 79.3, 76.8, 76.5, 76.3, 75.8, 75.2, 74.9, 74.1, 72.7, 72.6, 72.3, 71.2, 62.1, 54.5, 44.0, 38.0, 37.1, 32.9, 32.7, 29.9, 39.0, 27.9, 24.7, 21.8, 21.5, 21.0, 18.3, 15.8$ ppm; HRMS (FAB): *m/z* calcd for $C_{40}H_{60}O_{11}Na$ [M^++Na]: 739.4033; found: 739.4036.

28,29-Dihydro-30-desmethylgambierol (24): HF·pyridine (0.2 mL) was added to a solution of (*Z*)-vinyl bromide **29** (7.2 mg, 0.0058 mmol) in THF (0.6 mL) cooled to 0°C. The resulting mixture was stirred at room temperature for 4.5 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then $3 \rightarrow 5\%$ methanol/$CHCl_3$) to give a triol (4.3 mg, 92%) as an amorphous solid: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.33$ (dd, $J = 7.5, 1.5$ Hz, 1H), 6.15 (dd, $J = 7.5, 7.5$ Hz, 1H), 4.37 (ddd, $J = 7.5, 4.5, 1.5$ Hz, 1H), 3.94 (m, 1H), 3.79–3.76 (m, 2H), 3.70 (m, 1H), 3.65–3.58 (m, 2H), 3.48–3.40 (m, 3H), 3.34 (dd, $J = 11.0, 4.5$ Hz, 1H), 3.17–3.02 (m, 5H), 2.59 (m, 1H), 2.23 (ddd, $J = 12.0, 4.5, 4.0$ Hz, 1H), 2.12–2.07 (m, 2H), 2.02–1.42 (m, 20H), 1.32 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.22 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 134.9, 110.2, 84.7, 83.6, 82.4, 80.1, 79.9, 79.8, 79.1, 76.3, 75.84, 75.79, 75.2, 75.1, 74.4, 73.9, 73.5, 72.2, 71.9, 70.8, 62.8, 53.9, 43.6, 37.3, 35.5, 32.4, 32.1, 29.2, 28.5, 28.0, 26.9, 26.6, 24.2, 22.3, 20.3, 18.2, 16.1$ ppm.

CuCl (33.9 mg, 0.342 mmol), LiCl (22.1 mg, 0.521 mmol), and $[Pd(PPh_3)_4]$ (3.3 mg, 0.0029 mmol) were added to a solution of the above triol (4.3 mg, 0.0056 mmol) and (*Z*)-vinylstannane **23** (54.2 mg, 0.151 mmol) in degassed DMSO/THF (1:1, v/v, 1.5 mL). The resulting mixture was stirred at 60°C for 2 days and then quenched with 5% NH_4OH. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 3% methanol/$CHCl_3$) to give **24** (2.9 mg, 68%) as an amorphous solid: $[\alpha]_D^{30} = +8.0$ ($c = 0.12$ in CH_3OH); IR (film): $\tilde{\nu}_{max} = 3436, 2925, 2870, 1627, 1381, 1192, 1054\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.33–6.22$ (m, 2H), 5.70 (dddd, $J = 17.1, 10.1, 6.4, 6.4$ Hz, 1H), 5.49 (dd, $J = 17.1, 7.9$ Hz, 1H), 5.32 (dd, $J = 9.8, 8.5$ Hz, 1H), 4.95 (dd, $J = 17.1, 1.8$ Hz, 1H), 4.90 (dd, $J = 10.1, 1.5$ Hz, 1H), 4.25 (dd, $J = 8.5, 5.2$ Hz, 1H), 3.72–3.67 (m, 3H), 3.60 (m, 1H), 3.54–3.51 (m, 2H), 3.38–3.28 (m, 3H), 3.25 (dd, $J = 11.0, 4.9$ Hz, 1H), 3.08–2.91 (m, 5H), 2.85–2.83 (m, 2H), 2.14 (dd, $J = 11.9, 4.3$ Hz, 1H), 2.03–1.14 (m, 23H), 1.23 (s, 3H), 1.214 (s, 3H), 1.209 (s, 3H), 1.13 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 135.9, 131.7, 130.4, 125.8, 124.1, 115.4, 84.7, 82.4, 81.6, 80.4, 79.9, 79.1, 76.3, 75.9, 75.8, 75.2, 75.1, 75.0, 73.9, 73.5, 72.2, 72.0, 70.8, 70.5, 62.8, 53.9, 43.6, 37.3, 35.5, 32.4, 32.3, 31.7, 29.2, 28.52, 28.46, 27.1, 26.9, 24.2, 21.3, 20.3, 18.2, 16.1$ ppm; HRMS (FAB): *m/z* calcd for $C_{42}H_{64}O_{11}Na$ [M^++Na]: 767.4346; found: 767.4344.

28,29-Dihydrogambierol (25): Triethylamine (0.060 mL, 0.430 mmol) and the SO_3·pyridine complex (40.5 mg, 0.254 mmol) were added to a solution of alcohol **30** (20.1 mg, 0.0172 mmol) in CH_2Cl_2/DMSO (3:2, v/v, 1.25 mL) cooled to 0°C. The resulting mixture was stirred at 0°C for 40 min and then diluted with diethyl ether. The solution was washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude aldehyde, which was used in the next reaction without purification.

PPh_3 (93.5 mg, 0.356 mmol) was added to a solution of CBr_4 (57.8 mg, 0.174 mmol) in CH_2Cl_2 (1 mL) cooled to 0°C. The resulting mixture was stirred at 0°C for 30 min. Triethylamine (0.100 mL, 0.716 mmol) followed by a solution of the above aldehyde in CH_2Cl_2 (1 mL + 0.75 mL rinse) were added to this solution. The resulting mixture was stirred at 0°C for 30 min and then quenched with saturated aqueous $NaHCO_3$. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (eluted with 10% ether/benzene) and the eluent was concentrated to give a dibromoolefin, which was used in the next reaction without further purification.

nBu_3SnH (0.023 mL, 0.0855 mmol) and $[Pd(PPh_3)_4]$ (4.2 mg, 0.0036 mmol) were added to a solution of the above dibromoolefin in benzene (1 mL). After the resulting mixture was stirred at room temperature for 1 h, further nBu_3SnH (0.014 mL, 0.0520 mmol) and $[Pd(PPh_3)_4]$ (cat.) were added. This reaction mixture was stirred at room temperature for an additional 15 min and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $15 \rightarrow 30\%$ ether/hexanes) to give a (*Z*)-vinyl bromide (16.4 mg, 74% for the three steps) as a colorless oil: $[\alpha]_D^{30} = +8.5$ ($c = 0.48$, benzene); IR (film): $\tilde{\nu}_{max} = 2948, 2860, 1622, 1466, 1381, 1252, 1088, 834, 779, 703, 611\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.79–7.77$ (m, 4H), 7.23–7.22 (m, 6H), 5.92–5.88 (m, 2H), 4.56 (d, $J = 7.9$ Hz, 1H), 3.98 (dd, $J = 12.2, 3.9$ Hz, 1H), 3.88 (m, 1H), 3.71–3.64 (m, 4H), 3.48 (ddd, $J = 9.8, 9.5, 4.3$ Hz, 1H), 3.38–3.34 (m, 4H), 3.26 (m, 1H), 3.13–3.02 (m, 4H), 2.41 (ddd, $J = 7.6, 3.7, 3.7$ Hz, 1H), 2.31–2.26 (m, 2H), 2.13–1.92 (m, 7H), 1.85–1.35 (m, 14H), 1.31 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.17 (s, 9H), 1.12 (s, 3H), 1.08 (s, 3H), 1.00 (s, 9H), 0.98 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 136.0, 134.4, 133.3, 129.9, 128.3, 110.5, 86.3, 85.2, 82.9, 82.4, 80.8, 80.3, 79.7, 78.5, 77.1, 76.11, 76.07, 74.8 (\times 2), 74.1, 74.0, 72.7, 72.4 (\times 2), 64.3, 54.7, 44.4, 39.2, 38.6, 38.1, 32.9, 32.4, 30.4, 30.2, 29.2, 29.0, 28.3, 27.9, 27.1, 26.5, 26.2 (\times 2), 24.7, 22.1, 21.5, 19.5, 18.4, 16.4, -1.7, -2.0, -4.0, -4.9$ ppm; HRMS (FAB): *m/z* calcd for $C_{66}H_{105}{}^{79}BrO_{11}Si_3Na$ [M^++Na]: 1259.6046; found: 1259.6079; calcd for $C_{66}H_{105}{}^{81}BrO_{11}Si_3Na$ [M^++Na]: 1261.6046; found: 1261.6039.

HF·pyridine (0.25 mL) was added to a solution of this (*Z*)-vinyl bromide (13.2 mg, 0.0106 mmol) in THF (0.75 mL) cooled to 0°C. The resulting mixture was stirred at room temperature for 7 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then $1 \rightarrow 3\%$ methanol/$CHCl_3$) to give a triol (8.2 mg, quantitative) as an amorphous

solid: $[\alpha]_D^{29} = +112.6$ ($c = 0.11$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3440$, 2946, 2876, 1627, 1459, 1384, 1282, 1085, 1048, 912, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.39$ (d, $J = 7.3$ Hz, 1H), 6.14 (dd, $J = 8.2$, 7.3 Hz, 1H), 4.36 (d, $J = 8.2$ Hz, 1H), 3.78–3.75 (m, 2H), 3.69 (m, 1H), 3.64–3.59 (m, 2H), 3.47–3.39 (m, 3H), 3.34 (dd, $J = 10.4$, 4.6 Hz, 1H), 3.17–3.03 (m, 5H), 2.98 (m, 1H), 2.23 (ddd, $J = 11.9$, 4.0, 4.0 Hz, 1H), 2.12–2.09 (m, 2H), 2.02–1.43 (m, 21H), 1.32 (s, 3H), 1.30 (s, 6H), 1.22 (s, 3H), 1.17 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 132.7$, 110.7, 85.4, 84.9, 82.44, 82.36, 80.1, 79.9, 79.1, 76.4, 75.9, 75.8, 75.7, 75.2, 75.1, 74.2, 73.9, 72.2 (×2), 70.8, 62.8, 53.9, 43.6, 37.8, 37.4, 35.5, 32.4, 32.2, 29.2, 28.5, 27.8, 27.0, 26.0, 24.2, 21.3, 20.3, 18.3, 16.2 ppm; HRMS (FAB): m/z calcd for $C_{38}H_{57}{}^{79}BrO_{11}Na$ [M^++Na]: 791.3043; found: 791.3018; calcd for $C_{38}H_{57}{}^{81}BrO_{11}Na$ [M^++Na]: 793.2970; found: 793.2999.

CuCl (25.0 mg, 0.253 mmol), LiCl (13.0 mg, 0.307 mmol), and $[Pd(PPh_3)_4]$ (2.8 mg, 0.0024 mmol) were added to a solution of the above triol (3.2 mg, 0.0041 mmol) and (*Z*)-vinylstannane **23** (37.9 mg, 0.106 mmol) in degassed DMSO/THF (1:1, v/v, 1 mL). The resulting mixture was stirred at 60 °C for 2 days and then quenched with 5% NH_4OH. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 1→3→5% methanol/$CHCl_3$) to give **25** (2.0 mg, 64%) as an amorphous solid: $[\alpha]_D^{30} = +12.8$ ($c = 0.11$ in $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3437$, 2930, 2871, 1622, 1384, 1051 cm^{-1}; ^1H NMR (500 MHz, CD_3CN): $\delta =$ 6.46–6.36 (m, 2H), 5.84 (dddd, $J = 17.1$, 10.4, 6.4, 6.4 Hz, 1H), 5.55 (m, 1H), 5.37 (dd, $J = 10.4$, 10.4 Hz, 1H), 5.05 (dd, $J = 17.1$, 1.5 Hz, 1H), 4.98 (dd, $J = 10.4$, 1.5 Hz, 1H), 4.39 (d, $J = 8.9$ Hz, 1H), 3.75 (dd, $J = 11.9$, 4.3 Hz, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 3.55–3.33 (m, 6H), 3.21 (dd, $J =$ 11.0, 4.0 Hz, 1H), 3.18–3.13 (m, 2H), 3.04 (m, 1H), 3.00 (dd, $J = 12.8$, 3.4 Hz, 1H), 2.96–2.93 (m, 2H), 2.83 (m, 1H), 2.53 (m, 2H), 2.10 (m, 1H), 1.97–1.40 (m, 23H), 1.30 (s, 6H), 1.26 (s, 3H), 1.18 (s, 3H), 1.03 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta = 137.6$, 131.2, 130.6, 126.0, 125.6, 115.5, 85.6, 84.6, 82.9, 81.7, 80.9, 80.5, 79.8, 77.1, 76.8, 76.7, 75.9, 75.8, 75.5, 75.1, 74.6, 73.2, 72.8, 71.8, 62.5, 55.0, 44.1, 38.32, 38.26, 36.6, 33.3, 32.9, 32.3, 29.7, 29.3, 28.7, 27.9, 26.3, 25.0, 21.7, 20.8, 18.7, 16.5 ppm; HRMS (FAB): m/z calcd for $C_{43}H_{66}O_{11}Na$ [M^++Na]: 781.4503; found: 781.4478.

30-Desmethylgambierol (26): Triethylamine (0.023 mL, 0.236 mmol) and the SO_3·pyridine complex (29.1 mg, 0.183 mmol) were added to a solution of alcohol **33** (13.5 mg, 0.0118 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 1 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C for 30 min before dilution with diethyl ether. The solution was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude aldehyde, which was used in the next reaction without further purification.

PPh_3 (61.5 mg, 0.234 mmol) was added to a solution of CBr_4 (42.9 mg, 0.129 mmol) in CH_2Cl_2 (1 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Triethylamine (0.066 mL, 0.473 mmol) followed by a solution of the above crude aldehyde in CH_2Cl_2 (0.5 mL + 0.5 mL rinse) were added to this solution. The resultant mixture was stirred at 0 °C for 90 min and then quenched with saturated aqueous $NaHCO_3$. The solution was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (eluted with 10→15% ether/benzene) and the eluent was concentrated to give a dibromoolefin (7.3 mg, 47% for the two steps) along with alcohol **33** (6.8 mg, 50%). The dibromoolefin was used immediately in the next step without further purification.

nBu$_3$SnH (0.0065 mL, 0.0242 mmol) and a catalytic amount of $[Pd(PPh_3)_4]$ were added to a solution of the above dibromoolefin (7.3 mg, 0.0056 mmol) in benzene (1 mL). After stirring the resulting mixture at room temperature for 90 min, additional nBu$_3$SnH (0.0065 mL, 0.0242 mmol) and $[Pd(PPh_3)_4]$ (cat.) were added. After 30 min, further nBu$_3$SnH (0.0065 mL, 0.0242 mmol) and $[Pd(PPh_3)_4]$ (cat.) were added. The reaction mixture was stirred at room temperature for an additional 30 min and then concentrated under reduced pressure. The residue was filtered through a plug of silica gel (eluted with 25% ether/hexanes) and the eluent was concentrated to give (*Z*)-vinyl bromide, which was contaminated with over-reduced product.

HF·pyridine (0.1 mL) was added to a solution of the above material in THF (0.3 mL) cooled to 0 °C. The resulting mixture was stirred at room temperature for 3 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (eluted with 5% methanol/$CHCl_3$) and the eluent was concentrated to give the product, which was used in the next step without further purification.

CuCl (23.3 mg, 0.235 mmol), LiCl (13.0 mg, 0.307 mmol), and $[Pd(PPh_3)_4]$ (2.2 mg, 0.0019 mmol) were added to a solution of the above material and (*Z*)-vinylstannane **23** (35.8 mg, 0.100 mmol) in degassed DMSO/THF (1:1, v/v, 1 mL). The resulting mixture was stirred at 60 °C for 2 days and then quenched with 5% NH_4OH. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 1→3→5% methanol/$CHCl_3$) to give **26** (1.5 mg, 34% for the three steps) as an amorphous solid: $[\alpha]_D^{31} = -48.2$ ($c = 0.017$ in methanol); ^1H NMR (500 MHz, CD_3CN): $\delta = 6.47$ (dd, $J = 11.9$, 10.6 Hz, 1H), 6.34 (ddd, $J =$ 11.9, 10.7, <1 Hz, 1H), 5.87 (dddd, $J = 17.1$, 10.1, 6.4, 6.4 Hz, 1H), 5.66 (ddd, $J = 12.8$, 2.4, 2.4 Hz, 1H), 5.59–5.52 (m, 2H), 5.41 (dd, $J = 10.6$, 9.5 Hz, 1H), 5.05 (dd, $J = 17.1$, 1.5 Hz, 1H), 4.98 (dd, $J = 10.1$, 1.5 Hz, 1H), 4.16–4.12 (m, 2H), 4.05 (m, 1H), 3.75 (dd, $J = 11.6$, 4.6 Hz, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 3.51 (ddd, $J = 10.1$, 8.5, 4.9 Hz, 1H), 3.47–3.44 (m, 2H), 3.41–3.33 (m, 2H), 3.21 (dd, $J = 11.6$, 4.3 Hz, 1H), 3.20–3.13 (m, 2H), 3.07–3.01 (m, 2H), 2.96–2.94 (m, 2H), 2.89 (d, $J = 5.5$ Hz, 1H), 2.83 (s, 1H), 2.52 (t, $J = 5.5$ Hz, 1H), 2.09 (m, 1H), 1.97–1.70 (m, 8H), 1.65–1.40 (m, 11H), 1.30 (s, 6H), 1.26 (s, 3H), 1.19 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta = 137.5$, 135.5, 133.4, 131.8, 131.1, 127.7, 125.7, 115.6, 85.5, 82.9, 81.0, 80.8, 80.5 (×2), 80.1, 79.8, 77.1, 76.8, 75.9, 75.5, 74.6, 73.8, 73.6, 73.1, 72.6, 71.8, 62.5, 54.7, 44.1, 38.2, 36.6, 32.9, 32.8, 32.3, 29.7, 29.3, 27.9, 25.0, 21.7, 20.8, 18.6, 15.9 ppm; HRMS (FAB): m/z calcd for $C_{42}H_{62}O_{11}Na$ [M^++Na]: 765.4190; found: 765.4179.

6β-Alcohol 37: *N*-Methylmorpholine *N*-oxide (20.9 mg, 0.178 mmol), a catalytic amount of tetra-*n*-propylammonium perruthenate, and 4 Å molecular sieves were added to a solution of alcohol **36** (15.8 mg, 0.0136 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred at room temperature for 4 h and then directly subjected to flash chromatography (silica gel, 30% ethyl acetate/hexanes) to give a ketone (15.3 mg, 97%) as a colorless oil: $[\alpha]_D^{28} = +4.5$ ($c = 0.20$ in benzene); IR (film): $\tilde{\nu}_{max} = 2951$, 2862, 1738, 1645, 1465, 1384, 1256, 1092, 834, 777, 704 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.77$–7.76 (m, 4H), 7.25–7.23 (m, 6H), 5.79 (dd, $J = 13.2$, 2.3 Hz, 1H), 5.72 (d, $J = 13.2$ Hz, 1H), 4.34 (d, $J =$ 9.2 Hz, 1H), 4.16 (ddd, $J = 9.7$, 5.2, 4.6 Hz, 1H), 3.76–3.73 (m, 2H), 3.62–3.59 (m, 2H), 3.47–3.39 (m, 2H), 3.36–3.31 (m, 2H), 3.12 (dd, $J = 11.5$, 4.0 Hz, 1H), 3.09–3.02 (m, 5H), 2.43–2.39 (m, 3H), 2.20 (dd, $J = 15.5$, 11.5 Hz, 1H), 2.09–1.68 (m, 11H), 1.64–1.44 (m, 5H), 1.31 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.17 (s, 9H), 1.15 (s, 3H), 1.12 (s, 3H), 1.01 (s, 9H), 0.96 (s, 9H), 0.16 (s, 3H), 0.14 (s, 6H), 0.12 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 201.9$, 139.4, 136.0, 134.2, 130.5, 130.0, 128.5, 89.7, 85.1, 82.3, 81.9, 80.8, 80.2, 79.9, 79.8, 79.7, 78.7, 78.4, 76.9, 76.1, 75.0, 72.7, 72.6, 72.2, 63.9, 63.8, 54.5, 44.4, 44.0, 38.1, 32.60, 32.56, 28.9, 28.6, 27.4, 27.1, 26.1, 26.0, 24.7, 22.2, 21.6, 20.6, 19.4, 18.6, 18.31, 18.29, 15.7, −1.9, −2.1, −4.9, −5.1 ppm; HRMS (FAB): m/z calcd for $C_{65}H_{102}O_{12}Si_3Na$ [M^+ +Na]: 1181.6577; found: 1811.6609.

$NaBH_4$ (13.5 mg, 0.357 mmol) was added to a solution of the above ketone (84.5 mg, 0.0730 mmol) in methanol (5 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C for 25 min and then quenched with saturated aqueous NH_4Cl. The solution was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 20→30% ethyl acetate/hexanes) to give 6β-alcohol **37** (70.1 mg, 83%) as a colorless oil along with recovered **36** (9.9 mg, 12%). **37**: $[\alpha]_D^{28} = -8.9$ ($c = 0.21$ in benzene); IR (film): $\tilde{\nu}_{max} = 3399$, 2950, 2862, 1647, 1467, 1384, 1255, 1088, 834, 773, 704 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.78$–7.76 (m, 4H), 7.23–7.22 (m, 6H), 5.80 (dd, $J =$ 13.2, 2.9 Hz, 1H), 5.73 (d, $J = 13.2$ Hz, 1H), 4.35 (m, 1H), 4.16 (ddd, $J =$ 8.0, 6.3, 5.2 Hz, 1H), 3.78–3.75 (m, 2H), 3.65–3.62 (m, 2H), 3.51–3.44 (m, 3H), 3.36 (dd, $J = 10.9$, 5.2 Hz, 1H), 3.32 (m, 1H), 3.16–3.04 (m, 5H), 2.76 (dd, $J = 11.5$, 3.4 Hz, 1H), 2.45 (ddd, $J = 12.0$, 4.6, 4.0 Hz, 1H), 2.41

(ddd, $J=12.6$, 4.6, 4.6 Hz, 1H), 2.33 (dd, $J=11.5$, 4.0 Hz, 1H), 2.11–1.86 (m, 8H), 1.76–1.38 (m, 10H), 1.32 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.17 (s, 9H), 1.16 (s, 3H), 1.14 (s, 3H), 1.01 (s, 9H), 0.97 (s, 9H), 0.17 (s, 3H), 0.15 (s, 6H), 0.12 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta=139.4$, 136.0, 134.4, 130.5, 129.9, 128.5, 89.7, 85.1, 83.1, 82.3, 80.3, 80.0, 79.8, 79.7, 78.7, 77.8, 77.5, 77.0, 76.9, 76.1, 74.6, 72.8, 72.6, 72.2, 64.1, 63.9, 54.5, 44.6, 38.1, 37.5, 32.6, 32.3, 29.1, 29.0, 27.6, 27.1, 26.1, 26.0, 24.7, 22.5, 21.7, 19.4, 18.6, 18.31, 18.28, 16.3, 15.7, −1.9, −2.1, −4.9, −5.1 ppm; HRMS (FAB): m/z calcd for $C_{65}H_{104}O_{12}Si_3Na$ [M^++Na]: 1183.6733; found: 1183.6730.

6-*epi*-Gambierol (34): *N*-Methylmorpholine *N*-oxide (14.7 mg, 0.125 mmol), a catalytic amount of tetra-*n*-propylammonium perruthenate, and 4 Å molecular sieves were added to a solution of alcohol **39** (7.7 mg, 0.0066 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at room temperature for 25 min and then filtered through a plug of silica gel (eluted with ethyl acetate). The eluent was concentrated under reduced pressure to give crude aldehyde, which was immediately used in the next reaction.

PPh_3 (34.4 mg, 0.131 mmol) was added to a solution of CBr_4 (21.2 mg, 0.0639 mmol) in CH_2Cl_2 (0.75 mL) cooled to 0 °C was added. The resulting mixture was stirred at 0 °C for 30 min. Triethylamine (0.0400 mL, 0.287 mmol) followed by a solution of the above aldehyde in CH_2Cl_2 (0.75 mL + 0.5 mL rinse) were added to this solution. The resultant mixture was stirred at 0 °C for 40 min and then quenched with saturated aqueous $NaHCO_3$. The solution was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (eluted with 10% diethyl ether/benzene) and the eluent was concentrated to give dibromoolefin (7.7 mg, 0.0057 mmol), which was immediately used in the next reaction.

nBu$_3$SnH (0.0046 mL, 0.0171 mmol) and a catalytic amount of [Pd(PPh$_3$)$_4$] were added to a solution of the above dibromoolefin (7.7 mg, 0.0057 mmol) in benzene (1 mL). After stirring the mixture at room temperature for 2 h, further nBu$_3$SnH (0.0046 mL, 0.0171 mmol) and [Pd(PPh$_3$)$_4$] (cat.) were added. The reaction mixture was stirred at room temperature for an additional 30 min and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 10→15→20% ether/hexanes) to give a (*Z*)-vinyl bromide (5.2 mg, 64% for the three steps) as a colorless oil: $[\alpha]_D^{28}=-8.4$ ($c=0.119$ in benzene); IR (film): $\tilde{\nu}_{max}=2931$, 2858, 1621, 1465, 1381, 1254, 1081, 840, 773, 706, 607 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): $\delta=7.79$–7.77 (m, 4H), 7.24–7.22 (m, 6H), 6.12 (dd, $J=7.4$, 7.4 Hz, 1H), 6.02 (d, $J=7.4$ Hz, 1H), 5.90 (dd, $J=12.6$, 2.3 Hz, 1H), 5.76 (dd, $J=12.6$, 1.7 Hz, 1H), 4.53 (d, $J=7.4$ Hz, 1H), 4.35 (ddd, $J=9.2$, 2.3, 1.7 Hz, 1H), 3.68–3.66 (m, 2H), 3.61 (ddd, $J=10.9$, 9.2, 5.2 Hz, 1H), 3.55 (dd, $J=10.3$, 5.2 Hz, 1H), 3.45 (ddd, $J=10.3$, 9.2, 5.2 Hz, 1H), 3.37 (dd, $J=10.9$, 5.2 Hz, 1H), 3.24 (m, 1H), 3.12–3.09 (m, 4H), 3.05 (dd, $J=13.2$, 3.4 Hz, 1H), 2.76 (dd, $J=11.5$, 3.4 Hz, 1H), 2.45 (dd, $J=11.7$, 4.6 Hz, 1H), 2.37 (ddd, $J=8.0$, 8.0, 4.6 Hz, 1H), 2.28 (dd, $J=10.9$, 4.0 Hz, 1H), 2.08–1.94 (m, 7H), 1.80–1.74 (m, 3H), 1.68–1.51 (m, 6H), 1.45 (m, 1H), 1.39 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H), 1.17 (s, 9H), 1.14 (s, 6H), 1.06 (s, 9H), 0.94 (s, 9H), 0.25 (s, 3H), 0.17 (s, 3H), 0.11 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta=139.3$, 136.0, 134.4, 132.8, 131.1, 129.9, 128.5, 113.0, 85.1, 84.2, 83.1, 82.5, 80.23, 80.19, 80.0, 79.7, 78.6, 77.63, 77.61, 77.4, 77.0, 76.1, 74.3, 72.9, 72.6, 72.3, 64.2, 54.5, 44.5, 39.8, 38.1, 32.40, 32.37, 29.1, 29.0, 27.7, 27.1, 26.2, 26.0, 24.7, 22.2, 21.7, 19.4, 18.6, 18.31, 18.27, 16.3, 15.7, −1.8, −2.1, −3.7, −4.8 ppm; HRMS (FAB): m/z calcd for $C_{66}H_{103}{}^{79}BrO_{11}Si_3Na$ [M^++Na]: 1257.5889; found: 1257.5891; calcd for $C_{66}H_{103}{}^{81}BrO_{11}Si_3Na$ [M^++Na]: 1259.5890; found: 1259.5837.

HF·pyridine (0.2 mL) was added to a solution of the above (*Z*)-vinyl bromide (4.5 mg, 0.0037 mmol) in THF (0.6 mL) cooled to 0 °C. The resulting mixture was stirred at room temperature for 3 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 3→5% methanol/$CHCl_3$) to give a triol (2.9 mg, quantitative) as an amorphous solid: $[\alpha]_D^{28}=+23.4$ ($c=0.10$, $CHCl_3$); IR (film): $\tilde{\nu}_{max}=3416$, 2929, 2867, 1621, 1380, 1266, 1082, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.47$ (d, $J=7.4$ Hz, 1H), 6.22 (dd, $J=8.0$, 7.4 Hz, 1H), 5.75 (dd, $J=13.2$, 2.9 Hz, 1H), 5.50 (dd, $J=13.2$, 1.7 Hz, 1H), 4.36 (d, $J=8.0$ Hz, 1H), 4.20 (m, 1H), 3.64–3.61 (m, 3H), 3.52 (m, 1H), 3.47–3.40 (m, 2H), 3.34 (dd, $J=10.9$, 5.2 Hz, 1H), 3.16–3.10 (m, 3H), 3.06–3.01 (m, 2H), 2.98 (dd, $J=12.0$, 4.0 Hz, 1H), 2.22 (ddd, $J=11.5$, 4.6, 4.0 Hz, 1H), 2.15–2.06 (m, 2H), 2.02–1.84 (m, 6H), 1.73–1.45 (m, 11H), 1.31 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.22 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=$ 138.2, 131.6, 131.1, 112.7, 84.8, 83.9, 82.4, 81.6, 80.1, 79.9, 79.5, 79.4, 79.1, 77.8, 76.54, 76.49, 76.1, 75.8, 74.4, 72.2, 72.0, 71.8, 62.8, 53.7, 43.7, 37.4, 37.0, 32.4, 31.8, 29.7, 29.2, 28.6, 26.9, 24.2, 21.3, 18.2, 15.9, 15.6 ppm; HRMS (FAB): m/z calcd for $C_{38}H_{57}{}^{79}BrO_{11}Na$ [M^++Na]: 791.2982; found: 791.3021; calcd for $C_{38}H_{57}{}^{81}BrO_{11}Na$ [M^++Na]: 793.2970; found: 793.3018.

CuCl (28.3 mg, 0.286 mmol), LiCl (17.2 mg, 0.406 mmol), and [Pd(PPh$_3$)$_4$] (2.0 mg, 0.0017 mmol) were added to a solution of the above triol (2.9 mg) and (*Z*)-vinylstannane **23** (40.7 mg, 0.1136 mmol) in degassed DMSO/THF (1.1 mL). The resulting mixture was stirred at 60 °C for 2.5 days and then quenched with 5% NH_4OH. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 2→5% methanol/$CHCl_3$) to give **34** (2.2 mg, 80% for the two steps) as an amorphous solid: $[\alpha]_D^{28}=+4.3$ ($c=0.047$, $CHCl_3$); IR (film): $\tilde{\nu}_{max}=$ 3425, 2941, 2867, 1645, 1532, 1466, 1389, 1267, 1053, 752 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN): $\delta=6.45$ (dd, $J=11.6$, 11.1 Hz, 1H), 6.38 (dd, $J=11.6$, 11.4 Hz, 1H), 5.82 (dddd, $J=17.2$, 10.1, 6.3, 6.3 Hz, 1H), 5.71 (dd, $J=12.9$, 2.7 Hz, 1H), 5.54 (m, 1H), 5.46 (m, 1H), 5.38 (dd, $J=12.9$, 1.9 Hz, 1H), 5.05 (ddd, $J=17.2$, 3.5, 1.7 Hz, 1H), 4.98 (ddd, $J=10.1$, 3.5, 1.5 Hz, 1H), 4.31 (d, $J=8.9$ Hz, 1H), 4.21 (ddd, $J=9.4$, 2.7, 1.9 Hz, 1H), 3.53–3.39 (m, 6H), 3.34 (dd, $J=11.1$, 4.7 Hz, 1H), 3.19–3.13 (m, 3H), 3.06–2.93 (m, 5H), 2.82 (m, 1H), 2.62 (s, 1H), 2.56 (t, $J=5.4$ Hz, 1H), 2.10 (m, 1H), 1.97 (dd, $J=11.0$, 4.8 Hz, 1H), 1.94–1.89 (m, 3H), 1.85–1.77 (m, 4H), 1.65–1.33 (m, 11H), 1.30 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.17 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=140.3$, 138.7, 131.5, 131.1, 129.3, 127.5, 126.0, 115.6, 85.5, 83.1, 83.0, 81.9, 80.4, 80.3, 80.2, 79.7, 78.2, 78.0, 77.1, 76.9, 76.7, 76.4, 74.8, 73.1, 72.7 (×2), 62.4, 54.7, 44.6, 38.8, 38.2, 32.9, 32.2, 29.6 (×2), 29.3, 27.8, 25.0, 21.7, 21.3, 18.6, 16.2, 15.9 ppm; HRMS (FAB): m/z calcd for $C_{43}H_{64}O_{11}Na$ [M^++Na]: 779.4346; found: 779.4371.

6-Deoxygambierol (35): *N*-Methylmorpholine *N*-oxide (14.0 mg, 0.119 mmol), a catalytic amount of tetra-*n*-propylammonium perruthenate, and 4 Å molecular sieves were added to a solution of alcohol **42** (9.9 mg, 0.0096 mmol) in CH_2Cl_2 (1.5 mL). The resulting mixture was stirred at room temperature for 25 min and then filtered through a plug of silica gel (eluted with ethyl acetate). The eluent was concentrated under reduced pressure to give a crude aldehyde, which was immediately used in the next reaction.

PPh_3 (58.1 mg, 0.222 mmol) was added to a solution of CBr_4 (34.5 mg, 0.104 mmol) in CH_2Cl_2 (0.75 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C for 25 min. Triethylamine (0.0550 mL, 0.394 mmol) followed by a solution of the above aldehyde in CH_2Cl_2 (0.75 mL + 1.0 mL rinse) were added to this solution. The reaction mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous $NaHCO_3$. The solution was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (eluted with 10% ether/benzene) and the eluent was concentrated to give a dibromoolefin (9.1 mg, 0.0077 mmol), which was immediately used in the next reaction.

nBu$_3$SnH (0.0101 mL, 0.0385 mmol) and a catalytic amount of [Pd(PPh$_3$)$_4$] were added to a solution of the above dibromoolefin (9.1 mg, 0.0077 mmol) in benzene (1.2 mL). The resulting mixture was stirred at room temperature for 75 min and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30→35→40% ether/hexanes) to give a (*Z*)-vinyl bromide (7.3 mg, 66% for the three steps) as a colorless oil: $[\alpha]_D^{28}=+5.3$ ($c=0.087$ in benzene); IR (film): $\tilde{\nu}_{max}=2944$, 1631, 1459, 1382, 1255, 1079, 1029, 840, 705 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): $\delta=7.79$–7.77 (m, 4H), 7.24–7.22 (m, 6H), 6.12 (dd, $J=7.7$, 7.2 Hz, 1H), 6.02 (dd, $J=7.2$, 0.9 Hz, 1H), 5.89 (dd, $J=13.0$, 2.7 Hz, 1H), 5.75 (dd, $J=13.0$, 1.9 Hz, 1H), 4.52 (d, $J=7.7$ Hz, 1H), 4.34 (ddd, $J=9.5$, 2.7, 1.9 Hz, 1H), 3.72–3.65 (m, 2H), 3.59 (ddd, $J=10.9$, 9.6, 4.8 Hz, 1H), 3.43 (ddd, $J=10.6$, 8.7, 4.9 Hz, 1H), 3.35 (dd, $J=11.3$, 5.5 Hz, 1H), 3.26–3.18 (m, 2H), 3.17–3.01 (m, 5H), 2.45 (dd, $J=12.2$, 4.2 Hz, 1H), 2.36–2.33 (m, 2H), 2.07–1.87 (m, 6H), 1.80–1.23 (m, 13H),

1.39 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.18 (s, 9H), 1.13 (s, 3H), 1.12 (s, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ = 139.3, 136.0, 134.4, 132.8, 131.1, 129.9, 128.5, 113.0, 85.1, 84.2, 83.5, 82.7, 82.5, 80.2, 79.9, 79.7, 78.9, 78.6, 77.1, 76.1, 74.5, 73.7, 72.8, 72.5, 72.3, 64.2, 54.5, 44.7, 38.9, 38.2, 32.5, 32.4, 30.4, 29.2, 29.0, 28.4, 27.1, 26.0, 24.7, 22.2, 22.0, 20.8, 19.4, 18.3, 18.2, 15.7, −1.8, −2.1 ppm; HRMS (FAB): *m/z* calcd for $C_{60}H_{89}{}^{79}BrO_{10}Si_2Na$ [M^++Na]: 1127.5075; found: 1127.5110; calcd for $C_{60}H_{89}{}^{81}BrO_{10}Si_2Na$ [M^++Na]: 1129.5073; found: 1129.5061.

HF•pyridine (0.2 mL) was added to a solution of the above (*Z*)-vinyl bromide (7.3 mg, 0.0064 mmol) in THF (0.6 mL) cooled to 0 °C. The resulting mixture was stirred at room temperature for 4 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 2→4→6% methanol/$CHCl_3$) to give a triol (4.5 mg, 94%) as an amorphous solid: $[\alpha]_D^{27}$ = +7.2 (*c* = 0.067 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3437, 2937, 2875, 1645, 1464, 1386, 1268, 1074, 776, 677 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.47 (d, *J* = 6.9 Hz, 1H), 6.22 (dd, *J* = 8.6, 6.9 Hz, 1H), 5.75 (dd, *J* = 13.2, 2.9 Hz, 1H), 5.50 (dd, *J* = 13.2, 1.7 Hz, 1H), 4.36 (d, *J* = 8.6 Hz, 1H), 4.20 (ddd, *J* = 9.2, 2.9 1.7 Hz, 1H), 3.64–3.59 (m, 2H), 3.48–3.40 (m, 3H), 3.34 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.19–3.10 (m, 4H), 3.07–3.03 (m, 2H), 2.22 (ddd, *J* = 11.5, 4.6, 4.0 Hz, 1H), 2.15–2.07 (m, 2H), 2.02–1.89 (m, 4H), 1.84–1.34 (m, 15H), 1.314 (s, 3H), 1.309 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.22 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 131.6, 131.1, 112.7, 84.8, 83.8, 82.7, 82.2, 81.6, 79.8, 79.5, 79.3, 79.0, 76.6, 76.1, 75.8, 74.3, 73.5, 72.2, 72.0, 71.8, 62.9, 53.7, 43.8, 38.2, 37.4, 32.7, 31.8, 30.2, 29.4, 28.6, 27.6, 24.2, 21.5, 21.3, 20.4, 18.2, 15.6 ppm; HRMS (FAB): *m/z* calcd for $C_{38}H_{57}{}^{79}BrO_{10}Na$ [M^++Na]: 775.3033; found: 775.2999; calcd for $C_{38}H_{57}{}^{81}BrO_{10}Na$ [M^++Na]: 777.3021; found: 777.3036.

CuCl (34.9 mg, 0.353 mmol), LiCl (23.0 mg, 0.543 mmol), and $[Pd(PPh_3)_4]$ (4.2 mg, 0.0036 mmol) were added to a solution of the above triol (4.4 mg, 0.0059 mmol) and (*Z*)-vinylstannane **23** (52.5 mg, 0.147 mmol) in degassed DMSO/THF (1:1, v/v, 1.5 mL). The resulting mixture was stirred at 60 °C for 2 days and then quenched with 5% NH_4OH. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, $CHCl_3$ then 1→2→3% methanol/$CHCl_3$) to give **35** (3.3 mg, 76%) as an amorphous solid: $[\alpha]_D^{28}$ = +33.7 (*c* = 0.115 in benzene); IR (film): $\tilde{\nu}_{max}$ = 3433, 2941, 2874, 1631, 1452, 1380, 1268, 1073, 755 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN): δ = 6.45 (dd, *J* = 11.6, 10.9 Hz, 1H), 6.38 (dd, *J* = 11.6, 11.3 Hz, 1H), 5.83 (dddd, *J* = 17.1, 10.1, 6.3, 6.3 Hz, 1H), 5.70 (dd, *J* = 12.9, 2.7 Hz, 1H), 5.56 (m, 1H), 5.46 (dd, *J* = 10.9, 8.3 Hz, 1H), 5.38 (dd, *J* = 12.9, 1.9 Hz, 1H), 5.05 (ddd, *J* = 17.1, 3.5, 1.7 Hz, 1H), 4.98 (ddd, *J* = 10.1, 3.5, 1.5 Hz, 1H), 4.31 (d, *J* = 8.3 Hz, 1H), 4.21 (ddd, *J* = 9.4, 2.7, 1.9 Hz, 1H), 3.51 (ddd, *J* = 10.6, 8.8, 4.9 Hz, 1H), 3.47–3.39 (m, 4H), 3.34 (dd, *J* = 11.3, 4.9 Hz, 1H), 3.21 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.18–3.12 (m, 3H), 3.05–3.00 (m, 2H), 2.96–2.93 (m, 2H), 2.67 (s, 1H), 2.55 (t, *J* = 5.3 Hz, 1H), 2.08 (m, 1H), 1.96–1.83 (m, 4H), 1.78–1.40 (m, 17H), 1.30 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.21 (s, 3H), 1.20 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ = 140.6, 137.5, 131.5, 131.1, 129.3, 127.5, 126.0, 115.6, 85.6, 83.3, 83.1, 82.9, 82.0, 80.5, 80.2, 79.9, 79.7, 77.1, 76.8, 76.5, 75.0, 74.3, 73.1, 72.7 (×2), 62.5, 54.8, 44.7, 39.2, 39.3, 33.1, 32.9, 32.3, 30.8, 29.8, 29.4, 28.6, 25.0, 21.9, 21.4, 20.8, 18.7, 15.9 ppm; HRMS (FAB): *m/z* calcd for $C_{43}H_{64}O_{10}Na$ [M^++Na]: 763.4397; found: 763.4404.

Alcohol 46: HF•pyridine (0.15 mL) was added to a solution of tris-silyl ether **45** (11.1 mg, 0.0090 mmol) in THF (0.9 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C for 15 min and then warmed to room temperature. The reaction mixture was stirred for 3.5 h and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 20→40% ethyl acetate/hexanes) to give primary alcohol **46** (7.7 mg, 86%) as a colorless oil: $[\alpha]_D^{28}$ = +14.2 (*c* = 0.093 in benzene); IR (film): $\tilde{\nu}_{max}$ = 3436, 2929, 2857, 1623, 1465, 1382, 1255, 1078, 878, 777 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ = 6.11 (dd, *J* = 7.4, 6.9 Hz, 1H), 6.01 (d, *J* = 6.9 Hz, 1H), 5.89 (dd, *J* = 13.2, 2.9 Hz, 1H), 5.76 (dd, *J* = 13.2, 1.7 Hz, 1H), 4.52 (d, *J* = 7.4 Hz, 1H), 4.34 (m, 1H), 3.99 (dd, *J* = 12.6, 4.0 Hz, 1H), 3.85 (m, 1H), 3.65 (m, 1H), 3.58 (ddd, *J* = 10.9, 9.7, 5.2 Hz, 1H), 3.42–3.32 (m, 4H), 3.23 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.14–3.05 (m, 3H), 3.02 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.42 (ddd, *J* = 12.0, 4.6, 4.0 Hz, 1H), 2.35–2.28 (m, 2H), 2.14 (m, 1H), 2.10–1.94 (m, 6H), 1.77–1.36 (m, 11H), 1.39 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.00 (s, 9H), 0.94 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ = 139.3, 132.8, 131.1, 112.9, 85.1,84.2, 82.8, 82.5, 80.3, 79.9, 79.7, 78.6, 77.7, 76.1, 75.9, 74.9, 74.5, 74.1, 72.6, 72.5 (×2), 72.3, 62.7, 54.5, 44.3, 39.1, 38.1, 32.8, 32.4, 29.7, 29.0, 27.8, 26.1, 26.0, 24.7, 22.2, 22.0, 21.4, 18.4, 18.31, 18.27, 15.7, −1.8, −2.1, −4.0, −4.9 ppm; HRMS (FAB): *m/z* calcd for $C_{50}H_{85}{}^{79}BrO_{11}Si_2Na$ [M^++Na]: 1019.4712; found: 1019.4726; calcd for $C_{50}H_{85}{}^{81}BrO_{11}Si_2Na$ [M^++Na]: 1021.4705; found: 1021.4711.

1-*O*-Methylgambierol (43): HF•pyridine (0.2 mL) was added to a solution of methyl ether **47** (6.9 mg, 0.0068 mmol) in THF (0.6 mL) cooled to 0 °C. The resulting mixture was stirred at room temperature for 5 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 50→70→80% ethyl acetate/hexanes) to give a diol (5.2 mg, 98%) as an amorphous solid: $[\alpha]_D^{27}$ = +21.6 (*c* = 0.080 in $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3426, 2942, 2876, 1630, 1381, 1219, 1047, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.47 (d, *J* = 7.4 Hz, 1H), 6.22 (dd, *J* = 8.6, 7.4 Hz, 1H), 5.75 (dd, *J* = 13.2, 2.9 Hz, 1H), 5.50 (dd, *J* = 13.2, 1.7 Hz, 1H), 4.36 (d, *J* = 8.6 Hz, 1H), 4.20 (m, 1H), 3.76–3.72 (m, 2H), 3.69 (m, 1H), 3.48–3.40 (m, 2H), 3.38–3.34 (m, 3H), 3.32 (s, 3H), 3.29–3.10 (m, 3H), 3.08–3.03 (m, 2H), 2.23 (ddd, *J* = 12.0, 4.6, 4.0 Hz, 1H), 2.12–2.08 (m, 2H), 2.02–1.97 (m, 3H), 1.92–1.46 (m, 14H), 1.32 (s, 3H), 1.314 (s, 3H), 1.306 (s, 3H), 1.30 (s, 3H), 1.22 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 131.7, 131.1, 112.6, 84.8, 83.9, 82.5, 81.6, 79.9, 79.4, 79.1, 76.4, 76.1, 76.0, 75.8, 75.2, 74.6, 73.8, 72.6, 72.2, 72.0, 71.8, 70.8, 58.6, 53.7, 43.6, 37.3, 35.4, 32.2, 31.8, 28.5, 27.1, 25.8, 24.2, 21.33, 21.31, 20.3, 18.2, 15.6 ppm; HRMS (FAB): *m/z* calcd for $C_{39}H_{59}{}^{79}BrO_{11}Na$ [M^++Na]: 805.3138; found: 805.3157; calcd for $C_{39}H_{59}{}^{81}BrO_{11}Na$ [M^++Na]: 807.3127; found: 807.3096.

CuCl (30.8 mg, 0.311 mmol), LiCl (15.2 mg, 0.359 mmol), and $[Pd(PPh_3)_4]$ (2.7 mg, 0.0023 mmol) were added to a solution of the above diol (3.4 mg, 0.0043 mmol) and (*Z*)-vinylstannane **23** (62.3 mg, 0.174 mmol) in degassed DMSO/THF (1:1, v/v, 1.7 mL). After stirring the mixture at 60 °C for 2 days, the reaction was quenched with 5% NH_4OH. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 50→60% ethyl acetate/hexanes) to give **43** (2.9 mg, 88%) as an amorphous solid: $[\alpha]_D^{28}$ = +45.0 (*c* = 0.110 in benzene); IR (film): $\tilde{\nu}_{max}$ = 3427, 2943, 2873, 1631, 1385, 1268, 1072, 755 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN): δ = 6.46 (dd, *J* = 11.5, 10.9 Hz, 1H), 6.38 (dd, *J* = 11.5, 11.5 Hz, 1H), 5.83 (dddd, *J* = 17.2, 10.3, 6.3, 6.3 Hz, 1H), 5.70 (dd, *J* = 12.6, 2.3 Hz, 1H), 5.55 (m, 1H), 5.46 (m, 1H), 5.39 (dd, *J* = 12.6, 1.7 Hz, 1H), 5.05 (dd, *J* = 17.2, 3.5 Hz, 1H), 4.98 (dd, *J* = 10.3, 3.5 Hz, 1H), 4.31 (d, *J* = 8.0 Hz, 1H), 4.21 (m, 1H), 3.74 (dd, *J* = 12.0, 4.6 Hz, 1H), 3.67 (m, 1H), 3.59 (m, 1H), 3.51 (ddd, *J* = 10.3, 9.2, 5.2 Hz, 1H), 3.42 (ddd, *J* = 10.9, 9.7, 5.2 Hz, 1H), 3.36–3.30 (m, 3H), 3.29 (s, 3H), 3.23–3.13 (m, 3H), 3.07–3.00 (m, 2H), 2.96–2.93 (m, 2H), 2.82 (d, *J* = 1.8 Hz, 1H), 2.65 (s, 1H), 2.09 (m, 1H), 1.97–1.90 (m, 3H), 1.86–1.69 (m, 4H), 1.64–1.38 (m, 12H), 1.30 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H), 1.20 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ = 140.6, 137.5, 131.5, 131.1, 129.3, 127.5, 126.0, 115.6, 85.6, 83.1, 82.9, 81.9, 80.4, 80.2, 79.7, 77.0, 76.8, 76.7, 76.5, 75.9, 75.3, 74.5, 73.1 (×2), 72.7 (×2), 71.2, 58.5, 54.7, 44.1, 38.2, 36.6, 33.0, 32.9, 32.2, 29.3, 27.9, 26.4, 25.0, 21.7, 21.3, 20.8, 18.7, 15.9 ppm; HRMS (FAB): *m/z* calcd for $C_{44}H_{66}O_{11}Na$ [M^++Na]: 793.4503; found: 793.4524.

1-Deoxygambierol (44): HF•pyridine (0.3 mL) was added to a solution of compound **48** (10.6 mg, 0.0108 mmol) in THF (0.9 mL) cooled to 0 °C. The resulting mixture was stirred at room temperature for 5 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 40→60% ethyl acetate/hexanes) to give a diol (7.4 mg, 91%) as an amorphous solid: $[\alpha]_D^{28}$ = +35.5 (*c* = 0.110 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_6$): δ = 6.47 (d, *J* = 7.4 Hz, 1H), 6.22 (dd, *J* = 8.0, 7.4 Hz, 1H), 5.75 (dd, *J* = 12.6, 2.9 Hz, 1H),

5.50 (dd, $J=12.6$, 1.7 Hz, 1H), 4.35 (d, $J=8.0$ Hz, 1H), 4.20 (m, 1H), 3.76–3.69 (m, 3H), 3.48–3.40 (m, 2H), 3.34 (dd, $J=9.8$, 4.6 Hz, 1H), 3.18–3.10 (m, 3H), 3.08–3.03 (m, 2H), 2.23 (ddd, $J=11.5$, 4.6, 4.6 Hz, 1H), 2.12–2.08 (m, 2H), 2.02–1.81 (m, 5H), 1.77–1.35 (m, 12H), 1.32 (s, 3H), 1.31 (s, 3H), 1.30 (s, 6H), 1.22 (s, 3H), 0.88 ppm (t, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=138.2$, 131.6, 131.1, 112.6, 84.8, 83.9, 82.5, 81.6, 79.8, 79.4, 79.1, 76.3, 76.1, 76.0, 75.8, 75.2, 74.7, 73.8, 72.2, 72.0, 71.8, 70.9, 53.7, 43.6, 37.9, 37.3, 35.4, 31.8, 28.5, 27.1, 24.2, 21.32, 21.30, 20.3, 18.8, 18.2, 15.6, 14.0 ppm; HRMS (FAB): m/z calcd for $C_{38}H_{57}{}^{79}BrO_{10}Si_2Na$ [M^++Na]: 775.3033; found: 775.3008; calcd for $C_{38}H_{57}{}^{81}BrO_{10}Si_2Na$ [M^++Na]: 777.3021; found: 777.2978.

CuCl (42.9 mg, 0.433 mmol), LiCl (26.5 mg, 0.625 mmol), and $[Pd(PPh_3)_4]$ (6.2 mg, 0.0054 mmol) were added to a solution of the above diol (5.2 mg, 0.0069 mmol) and (*Z*)-vinylstannane **23** (105.1 mg, 0.2935 mmol) in degassed DMSO/THF (1:1, v/v, 3 mL). The resulting mixture was stirred at 60 °C for 2 days and then poured into cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30→35→40% ethyl acetate/hexanes) to give **44** (4.6 mg, 90%) as an amorphous solid: $[\alpha]_D^{28}=+19.2$ ($c=0.15$ in benzene); IR (film): $\tilde{\nu}_{max}=3340$, 2950, 2874, 1730, 1631, 1458, 1384, 1266, 1078, 806, 752, 679 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN): $\delta=6.46$ (dd, $J=11.5$, 11.5 Hz, 1H), 6.38 (dd, $J=11.5$, 10.9 Hz, 1H), 5.83 (dddd, $J=17.2$, 10.3, 6.3, 6.3 Hz, 1H), 5.70 (dd, $J=13.2$, 2.9 Hz, 1H), 5.56 (m, 1H), 5.46 (dd, $J=10.9$, 8.0 Hz, 1H), 5.39 (dd, $J=13.2$, 1.7 Hz, 1H), 5.05 (dd, $J=17.2$, 3.5 Hz, 1H), 4.98 (dd, $J=10.7$, 3.5 Hz, 1H), 4.31 (d, $J=8.0$ Hz, 1H), 4.21 (m, 1H), 3.74 (dd, $J=11.5$, 4.6 Hz, 1H), 3.67 (m, 1H), 3.59 (m, 1H), 3.51 (ddd, $J=10.3$, 9.2, 5.2 Hz, 1H), 3.42 (ddd, $J=10.9$, 9.7, 5.2 Hz, 1H), 3.34 (dd, $J=10.9$, 4.6 Hz, 1H), 3.23–3.13 (m, 3H), 3.07–3.00 (m, 2H), 2.96–2.93 (m, 2H), 2.82 (m, 1H), 2.65 (s, 1H), 2.10 (m, 1H), 1.97–1.90 (m, 6H), 1.86–1.77 (m, 3H), 1.70–1.26 (m, 10H), 1.30 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 0.87 ppm (t, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta=140.8$, 137.7, 131.7, 131.2, 129.5, 127.6, 126.2, 115.7, 85.7, 83.3, 83.1, 82.1, 80.6, 80.4, 79.9, 77.2, 76.9 (×2), 76.6, 76.0, 75.4, 74.7, 73.3, 72.8 (×2), 71.9, 54.9, 44.3, 38.7, 38.4, 36.7, 33.0, 32.4, 29.5, 28.1, 25.1, 21.9, 21.5, 21.0, 19.6, 18.1, 16.1, 14.5 ppm; HRMS (FAB): m/z calcd for $C_{43}H_{64}O_{10}Na$ [M^++Na]: 763.4397; found: 763.4423.

Mouse toxicity assay: All the synthetic analogues were purified by HPLC (Asahipak ODP-506D, ϕ 4.6×150 mm, CH_3CN/H_2O as eluent, λ 210 nm). Each sample was dissolved in 1% Tween 60 (0.5–0.8 mL) by sonication and intraperitoneally injected into a ddY strain male mouse (12–17 g body weight).

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