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Total Synthesis of Gambierol: The Generation of the A–C and F–H Subunits by Using a C-Glycoside Centered Strategy

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Abstract: Gambierol, a representative of the marine ladder toxin family, consists of eight ether rings, 18 stereocenters, and two challenging pyranyl rings having methyl groups that are in a 1,3-diaxial orientation to one another. Herein we describe the generation of gambierol's A–C and F–H ring systems and demonstrate the versatility of the glycosyl anhydride, enol ether–olefin RCM strategy to fused polycyclic ethers. This work has both enabled us to generate sufficient quantities of the gambierol precursors and has enabled us to better understand the chemical transformations that were key to these efforts. Fundamental work included efforts to C-glycosides and C-ketosides, Claisen rearrangements, and enol ether–olefin RCM reactions.

Keywords: gambierol · glycosides · metathesis · natural products · total synthesis

Introduction

The marine ladder toxin family consists of structurally interesting polycyclic ether containing natural products.[1,2] Representative is gambierol (Figure 1), a ladder toxin the structure of which was first reported in 1993 by Yasumoto and co-workers from the cultured cells of *Gambierdiscus toxicus*, the organism responsible for ciguatera poisoning.[3] Architecturally, gambierol consists of eight ether rings, 18 stereocenters, and two challenging pyranyl rings having methyl groups that are in a 1,3-diaxial orientation to each other.

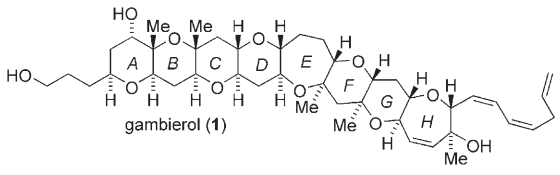

Figure 1.

Equally intriguing to their structures are the biological properties of the polyethers. Although commonly associated with neurotoxicity in the form of ciguatera (ciguatoxin),[4] red tides (brevetoxins),[5] and diarrhetic shellfish poisoning (yessotoxin),[6] recent reports have described other phenomena.[7] Gambierol's properties are typical of the neurotoxic members of this family; it has demonstrated neurotoxicity in mice (LD_{50} 50 $\mu g\,kg^{-1}$) targeting the lungs, heart, and stomach.[8] Its symptoms are similar to those seen with the ciguatoxins inferring the possibility that gambierol is involved in ciguatera poisoning.[9] As with the other neurotoxic members of this family, it is believed that gambierol's symptoms arise from its ability to bind to ion channels. This has, in fact, been demonstrated: Yasumoto, Hirama, and co-workers have shown that gambierol inhibits the binding of brevetoxin PbTx-3 to its target, site 5 of voltage gated sodium channels;[10] Bigiani, Sasaki, and co-workers demonstrated that gambierol is capable of binding to potassium channels.[11]

Results and Discussion

As a result of its biology and relatively complex molecular structure, gambierol has attracted the attention of synthetic chemists worldwide.[12] This attention has resulted in the completion of three total syntheses. The Sasaki group utilized their Suzuki coupling strategy to complete the first total

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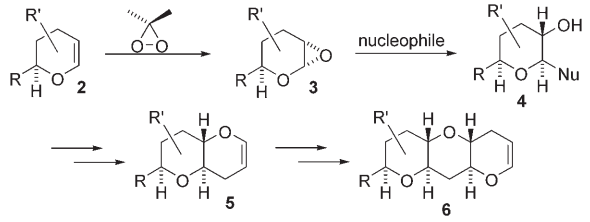
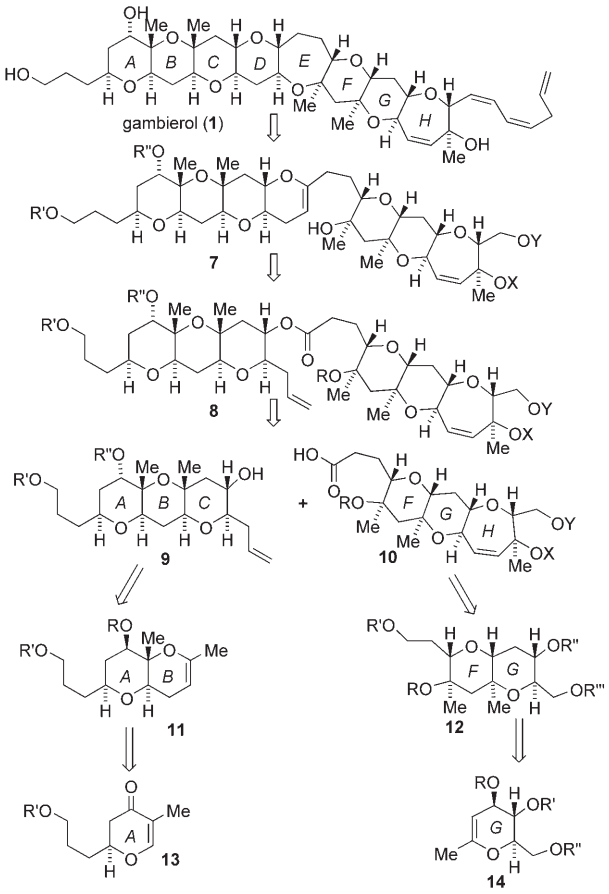
synthesis of gambierol.[13] Shortly thereafter, the Yamamoto group completed the second synthesis using their intramolecular allylstannane cyclization chemistry.[14] The third synthesis is described herein and in the adjoining manuscript.[15]

We decided to employ an iterative strategy to the synthesis of gambierol that centers on the generation of C-glycosides from cyclic enol ethers (Scheme 1). Although this approach had been reasonably successful for us previously, it was clear that gambierol's octacyclic core and 18 stereocenters would present unique challenges that would test its scope and limitations.[16]



Scheme 1. Generation of C-glycosides from cyclic enol ethers.

Our analysis of gambierol is outlined in Scheme 2. We opted to employ a convergent approach where the iterative C-glycoside strategy outlined above would be used to both generate and couple two nearly equal subunits (e.g. **9** + **10** → **8** → **7** → **1**). Described in this manuscript is our synthesis of the A–C (i.e., **9**) and F–H (i.e., **10**) ring precursors.[17] The adjoining manuscript describes the coupling of the precursors and the completion of gambierol.[18]



Scheme 2. Retrosynthetic analysis.

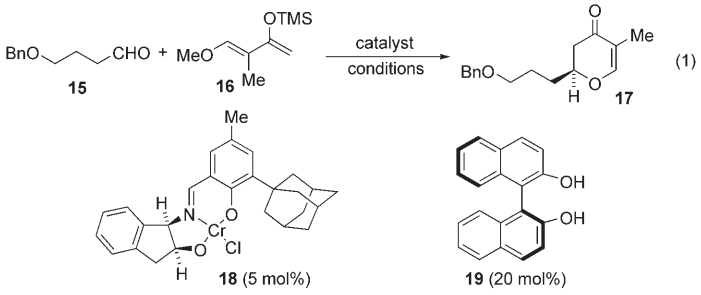
A–C Gambierol subunit

A-Ring: Our synthesis of the gambierol A–C subunit began with the A-ring and an asymmetric hetero-Diels–Alder cycloaddition reaction.[19] Our initial experiments explored the use of Keck's titanium BINOL protocol because of the success observed using it to catalyze the analogous reaction between Danishefsky's diene and **15**.[20,21] In contrast to these results, no cycloadduct was observed when methyl-substituted diene **16**[22] was subjected to **15**, BINOL, and [Ti(O*i*Pr)$_4$] (Table 1, entry 2).[23] Other Lewis acid–BINOL complexes gave moderate yields of cycloadduct; the cycloadduct was formed racemically or in low enantiomeric excess (Table 1, entries 3 and 4).[24]

With the failure of the BINOL complexes to catalyze the asymmetric reaction between **15** and **16**, we turned to other catalysts and became intrigued by reports of the use of Jacobsen's tridentate Cr^{III} catalyst **18** [Eq. (1)] in hetero-Diels–Alder reactions.[25] To our delight, **18** catalyzed the reaction between **15** and **16** to give cycloadduct **17** in both high yield and enantiomeric purity (Table 1, entry 1).[26]

Having established an effective route to pyranone **17**, we planned to use the newly established C(4) stereocenter to generate the remaining A–C stereocenters. These efforts

Table 1. Influence of adamantane catalyst **18** and BINOL (**19**) derived catalysts on the hetero-Diels–Alder cycloaddition of **15** and **16**.

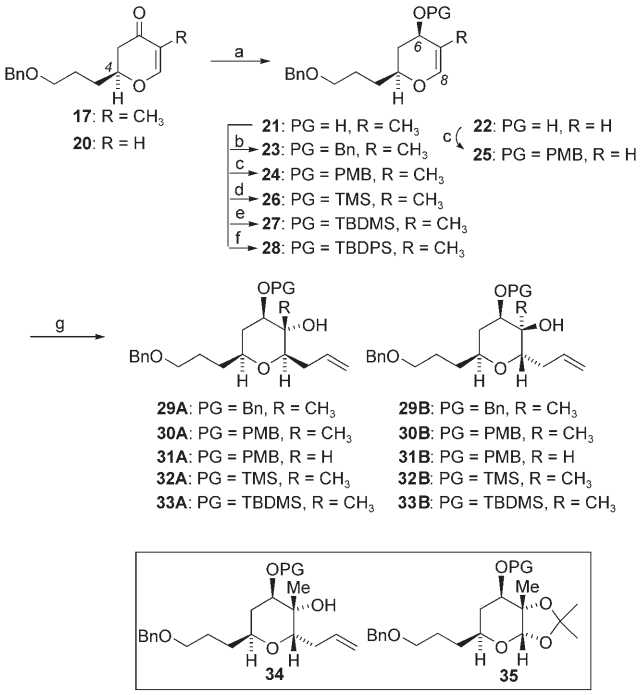


(1)

Entry	Catalyst	Conditions	Yield [%]	*ee* [%]
1	**18**	4 Å MS, RT, 70 h; TFA, 0 °C, CH_2Cl_2, 1 h	90	94
2	**19**	[Ti(O*i*Pr)$_4$]; TFA	0	–
3	**19**	B(OMe)$_3$	69	0
4	**19**	AlMe$_3$	20	8

began with the reduction of the C(6) ketone using Luche conditions to give the corresponding ether after protection of the C(6) alcohol (Scheme 3).[27] That the C(6) stereocenter from this reaction was epimeric to that needed for gambierol was intentional; we planned to use this center to con-

trol the formation of the C(7) and C(8) centers in the subsequent β-C-glycoside forming chemistry. To this goal, exposure of **23** and **24** to dimethyl dioxirane (DMDO) and propenyl magnesium chloride resulted in the generation of a mixture of C-glycoside diastereomers favoring the desired isomers **29A** and **30A**, respectively.[28] Although **29A** and **30A** were isolated in useful quantities, it was surprising that this reaction was not more selective; PMB ether **25**,[29] which lacks a C(7) alkyl substituent, gave β-C-glycoside **31** in 95% yield and with >95:5 diastereoselectivity.[30]



Scheme 3. Synthesis of the A-ring fragments **29** and **30**. a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH 0°C; b) NaH, BnBr, TBAI, THF (92%, 2 steps); c) NaH, PMBCl, DMF (95%, two steps); d) TMSCl, imidazole, DMF; e) TBDMSCl, imidazole, DMAP, DMF; f) TBDPSCl, NEt_3, DMAP, DMF; g) DMDO, CH_2Cl_2 (−65°C to RT); propenyl magnesium chloride, THF, (−65°C to RT), see Table 2.

The ether substituent at C(6) also influenced the effectiveness of the C-glycoside forming chemistry. Glycals containing C(6) silyl ethers reacted much more sluggishly and with even lower diastereoselectivity than the corresponding C(6) benzyl ethers (Table 2, entries 4–6).

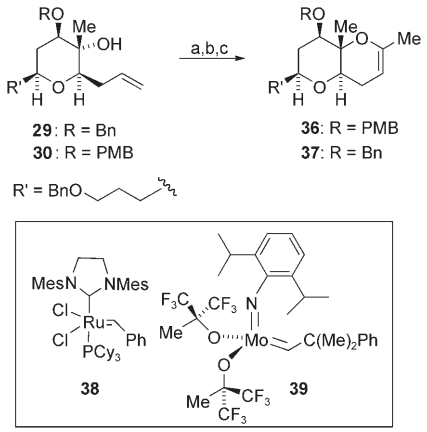
B-Ring: Having found a reasonable route to the A-ring, we turned our attention to the B-ring. We intended to utilize an enol ether–olefin ring closing metathesis (RCM) sequence to convert the olefinic alcohols **29** and **30** into the corresponding cyclic enol ether followed by a C-ketoside forming reaction to generate the C(10) and C(11) stereocenters.[31,32] Required for the metathesis sequence was the conversion of **29** and **30** into the corresponding acyclic enol ether via the corresponding ester (Scheme 4, Table 3). From the variety of methods to carry out this conversion (most involving the use of titanium reagents), we have had the most success with the Takai–Utimoto reagent.[33] When compared with other titanium alkylidenes, the advantages of this reagent include that the active titanium alkylidene reagent is generated in situ and that the reactivity of the reagent falls somewhere between the more commonly used Tebbe and Petasis reagents. When the olefinic acetate from **29** or **30** was subjected to the Takai–Utimoto reagent a 1:1 mixture of cyclic and acyclic products were isolated (Scheme 4).[34] That mixtures were obtained in these reactions was not a problem, the mixtures were simply subjected to the Schrock Mo catalyst **39** or the Grubbs II catalyst **38** to cyclize the remaining acyclic material.

Having generated the requisite B-ring enol ether, we turned our attention to the formation of the B-ring C-keto-

Table 2. Conversion of enol ethers **23**–**28** into C-glycosides **29**–**33**.

Entry	Enol ether	C-glycoside	**A**/**B**[a]	Yield [%]
1	**23**	**29**	7.5:1[b]	90
2	**24**	**30**	7.5:1[b]	78
3	**25**	**31**	>95:5	95
4	**26**	**32**	2:1[c]	20
5	**27**	**33**	2:1[c]	46
6	**28**	–	–	<5

[a] Ratio was determined from 1H NMR of crude reaction mixture. [b] Also isolated 5% of diastereomeric glycoside **34**. [c] Major by-product was acetone adduct **35**.



Scheme 4. a) Ac_2O, Hünigs base; b) $TiCl_4$, CH_2Br_2, $PbCl_2$, TMEDA, Zn, THF, CH_2Cl_2; c) RCM (see Table 3).

Table 3. Conversion of A-ring substrates **30** and **29** into cyclic enol ethers **36** and **37**, respectively.

Entry	ROH	R	Yield (acetate) [%]	RCM catalyst Conditions	Yield (RCM) [%][a,b]
1	**29**	PMB	77	**38** (20%), PhH, RT	74
2	**29**	PMB	77	**39** (20%), hexanes, 65°C	70
3	**30**	Bn	85	**38** (10%), PhH, RT	80

[a] Takai protocol gave a 1:1 mixture of cyclic and acyclic enol ethers. [b] Two steps.

side. From the outset, we had viewed the generation of this ketoside to be a challenge as it required the stereoselective addition of a carbon nucleophile to the more substituted end of the anhydride. In spite of this concern, we were hopeful that we would be able to overcome any problems that might arise because of the high degree of flexibility in the anhydride coupling sequence.[35]

In the event, the sequential treatment of **37** with DMDO and propenyl magnesium chloride gave a modest yield of C-ketoside **41** having the undesired C(11) stereochemistry [Eq. (2), Table 4]. Interestingly, the coupling reaction had occurred from the same face as the angular methyl group in **42** (Figure 2) implying a direct addition of the nucleophile

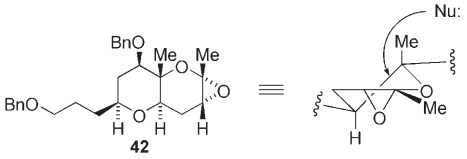
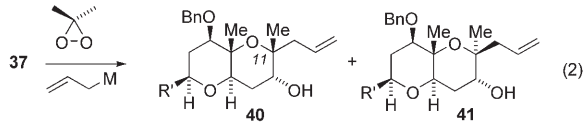


Figure 2.

to the anhydride rather than via the intermediacy of an oxocarbenium ion as had been anticipated. In an attempt to force the reaction of **42** to proceed through the desired intermediate, we examined the coupling of **42** with triallyl aluminum and triallyl borane. Unfortunately, the use of these reagents resulted in the generation of gross mixtures of stereoisomeric C-ketosides.[36] Clearly, our concerns about the use of anhydrides to generate the gambierol B-ring had proved themselves to be well founded.

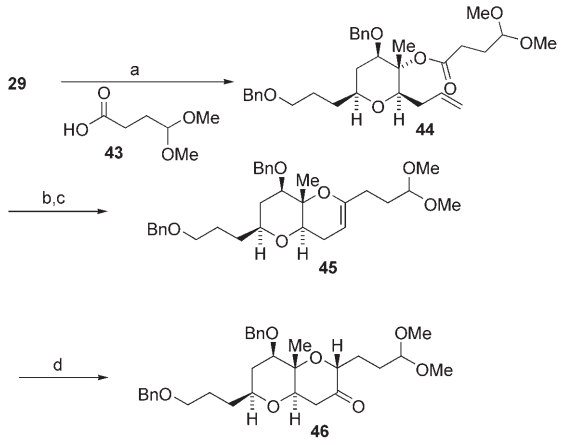
Table 4. The coupling of propenyl nucleophiles with anhydride **42**.



Entry	M	**40**:**41**	Yield [%]
1	MgCl	<5:95	50
2	$B(allyl)_2$	1:1.5	45
3	$Al(allyl)_2$	1.5:1	48

The relatively low yields observed in the reactions of **37** were probably a consequence of the instability of anhydride **42**. Ring-opening of the presumed ground state conformer proceeds through a chair transition state giving *trans*-diaxial addition products (Figure 2). Consequently, relatively weak nucleophiles (i.e., acetone) were capable of decomposing this substrate.[37]

In light of the direct addition of propenyl magnesium chloride to **42**, the simple reversal of the order of the C(11) C–C bond formation might solve the problem of establishing the C(11) center (Scheme 5). That is, the incorporation of a C-ring precursor into the B-ring anhydride and the coupling of this species with methyl magnesium chloride would, in theory, result in the desired adduct. Unfortunately, this strategy was also unsuccessful and instead gave ketone **46** from a stereoselective hydride migration in 75% yield.[38] The enhanced yield in this reaction is probably the result of our not concentrating the intermediate anhydride as a result of using Messeguer's "acetone free" dimethyl dioxirane that can be generated as an $\approx$0.2 M solution in CH_2Cl_2.[39]



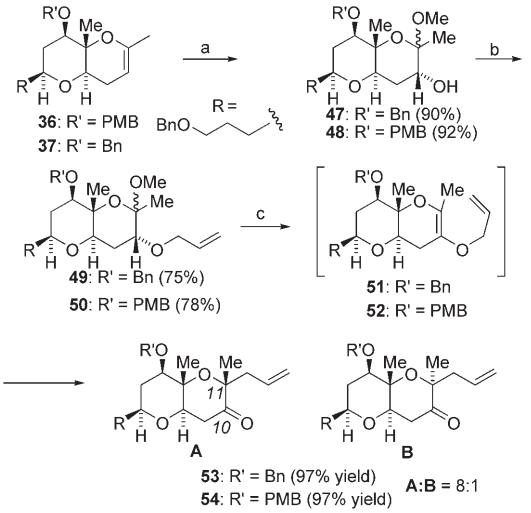
Scheme 5. a) DCC, DMAP, CH_2Cl_2 (64%); b) $TiCl_4$, $PbCl_2$, CH_2Br_2, TMEDA, Zn, THF, CH_2Cl_2; c) **38** (20%), PhH, RT (62%, two steps); d) DMDO, CH_2Cl_2, MeMgCl, THF, −60 °C (75%).

Following the disappointing results mentioned above, it was apparent that a reassessment of our synthetic plans to the C(11) ketoside was needed. Among the various possibilities, we became intrigued with the possibility of exchanging an intramolecular C–C bond forming reaction for the intermolecular variant that we had been attempting. More specifically, we became interested in employing a C(10) allyl vinyl ether in a Claisen rearrangement to generate the C(11) ketoside. Although related rearrangements had been utilized to generate C-glycosides, all previous examples that we are aware of had come from precursors having the allylic component as part of the pyranyl ring system. In these cases, the control of the C-glycoside center was predetermined by the stereochemistry of the allylic center.[40] In our substrate, we hoped that subtler influences would control the outcome of the reaction. Namely, we envisioned that the C(7) angular methyl and/or the *trans*-pyranyl ring system would direct the generation of the new C(11) stereocenter. That the proposed reaction would lead to a C(10) ketone was an added benefit as it would enable us to avoid a subsequent epimerization reaction; reduction of the ketone from the axial face would result in the desired C(10) alcohol.

The execution of the strategy began with the epoxidation of **36** and **37** by using *m*-CPBA in methanol to give ketals **47** and **48**, respectively, as a 2:1 mixture of anomers in high yield (Scheme 6). These were then converted into allyl ethers **49** and **50** using standard conditions. We were pleased to isolate C-ketosides **51** and **52**, each as an 8:1 mixture of diastereomers and in 97% yield, when **47** and **48** were subjected to PPTS and pyridine at 100 °C. Not only had the

PPTS conditions generated the enol ether but they had also induced the desired rearrangement.

Presumably, the C(11) stereocenter resulted from a chair-like transition state to give the *trans*-pyranyl system as indicated by **55** (Figure 3). Rearrangement to the opposite face would suffer from steric interactions between the angular methyl group and the side chain.



Scheme 6. a) *m*-CPBA, MeOH; b) propenyl bromide, NaH, THF; c) PPTS, pyridine, 100 °C.

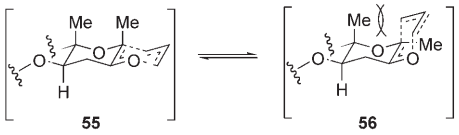
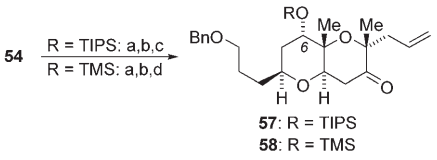


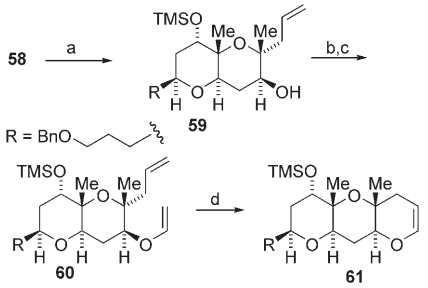
Figure 3.

Having finally solved the C(11) problem, we next turned to the inversion of the C(6) stereocenter. This was accomplished using standard conditions; namely, oxidative removal of the PMB ether, Mitsunobu inversion, and silyl ether formation (Scheme 7). We examined β-PMB ether **54**, α-TMS ether **58**, and α-TIPS ether **57** in the subsequent chemistry.



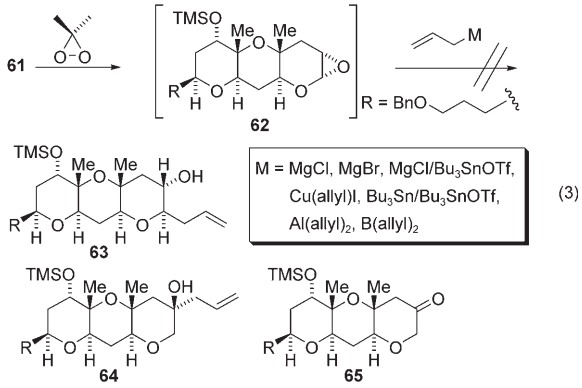
Scheme 7. a) DDQ, CH_2Cl_2/H_2O (97%); b) DEAD, PPh_3, *p*-$NO_2C_6H_4CO_2H$, $PhCH_3$; NaOH, THF, MeOH (80%); c) TIPSOTf, 2,6-lutidine, DMAP DMF (100%); d) TMSOTf, NEt_3, DMF (97%).

C-Ring: The most direct route to the C-ring and the A–C coupling precursor from **54**, **57**, or **58** would involve the generation of the corresponding unsubstituted enol ether (e.g. **61**) and its subsequent conversion to an allylic alcohol (e.g. **63**). TMS bicycle **58** was used to examine the feasibility of this approach. Reduction of the ketone from the axial face and opposite the C(7) methyl group provided alcohol **59** (Scheme 8). Vinyl ether formation gave metathesis precursor **60**.[41] Enol ether–olefin RCM provided **61** as the precursor to the C ring.



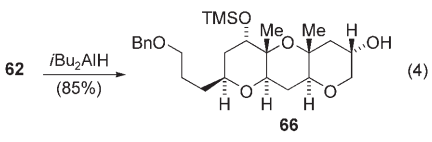
Scheme 8. a) $NaBH_4$, EtOH (100%); b) TsOH, ethyl vinyl ether, methyl *tert*-butyl ether, −60 to 0 °C (95%); c) TMSOTf, NEt_3, CH_2Cl_2, 0 °C (98%); d) **38** (20 mol%), PhH, RT (95%).

Unfortunately, all attempts to couple the anhydride from **61** (i.e., **62**) with allyl nucleophiles failed to deliver the desired allyl C-glycoside. Instead we isolated a considerable amount of ketone **65** [Eq. (3)] resulting from a 1,2-hydride migration or tertiary alcohol **64** from allyl addition to the ketone.[42]



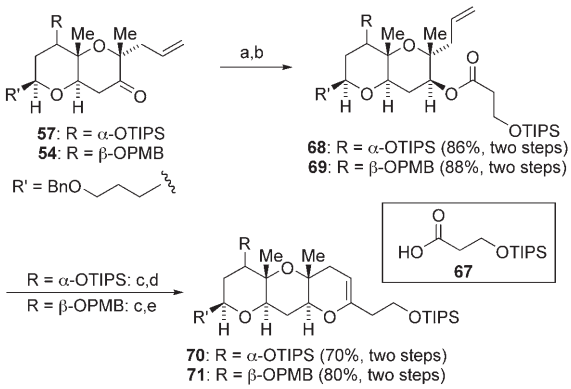
(3)

Although the results with allylic nucleophiles were disappointing, we were encouraged by our ability to efficiently reduce **62** using DIBAL-H to give **66** as this reaction ultimately led to a solution to the generation of the C-ring stereocenters [Eq. (4)].



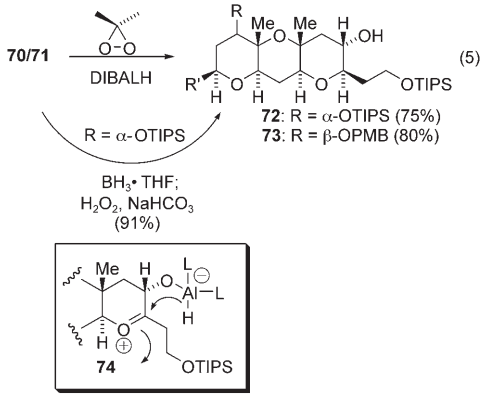
(4)

We became intrigued with the notion of using the DIBAL-H reduction sequence on an appropriately substituted anhydride to generate the desired compound. To this end, the exposure of esters **68** and **69** to the Takai–Utimoto protocol gave mostly acyclic enol ether along with approximately 8% of cyclic enol ethers **70** and **71**, respectively (Scheme 9).[43] As described previously, the presence of the mixture was of no consequence; enol ether–olefin RCM was used to cyclize the remaining acyclic material.

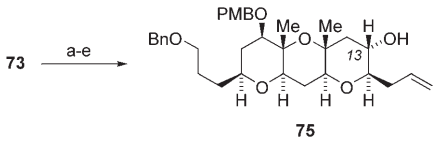


Scheme 9. a) $NaBH_4$, EtOH; b) DCC, DMAP, **65**; c) CH_2Br_2, CH_2Cl_2, $TiCl_4$, Zn, $PbCl_2$, TMEDA, THF; d) **38** (20 mol%), PhH, RT; e) **39** (20 mol%), hexanes, 60 °C.

The final C-ring stereocenters were incorporated either using the anhydride formation, directed reduction strategy (β-OPMB substrate **71**) or using a hydroboration, oxidation reaction [α-OTIPS substrate **70**, Eq. (5)].[44] Presumably, the C(11) angular methyl group directs the oxidation reaction; as has been discussed previously we believe that the stereochemical outcome of the anhydride reduction sequence is a result of a directed reduction via an aluminum ate complex (i.e., **74**).[45]



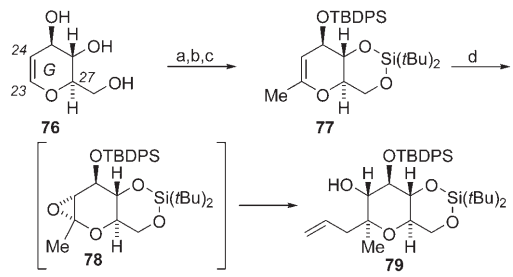
Our initial subunit coupling reactions were carried out on β-OPMB derivative **75**; its synthesis from **73** is illustrated in Scheme 10. Generation of the C(13) pivaloyl ester was followed by TIPS ether hydrolysis using TBAF. Oxidation of the resulting primary alcohol and hydrolysis of the ester gave the corresponding hydroxy aldehyde. Wittig olefination completed our synthesis of A–C coupling precursor **75**.



Scheme 10. a) PivCl, DMAP, pyridine, CH_2Cl_2 (90%); b) TBAF, THF (93%); c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2 (98%); d) LiOH, MeOH; silica gel (90%); e) $Ph_3P{=}CH_2$, THF (92%).

F–H Subunit: With a reasonable synthesis of the A–C coupling precursor in hand, we set our sights on the generation of the gambierol F–H subunit. At the outset of this work, we anticipated that the biggest challenge would be the F- and G-rings where we were again faced with the generation of a C-ketoside. In spite of the fact that we had been largely unsuccessful in our previous attempts to use α-substituted anhydrides as direct precursors to ketosides,[46] the potential efficiency of the anhydride to ketoside approach convinced us that it deserved further examination.

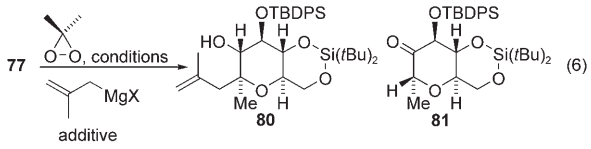
G-Ring: We selected bis-silyl D-glucal derivative **77** as a precursor to the G-ring (Scheme 11). Not only would the C(25) stereocenter serve as a handle for the introduction of the C(23) and C(24) centers but the C(26) and C(27) centers would come directly from D-glucal. The choice of TBDPS and cyclic silylene were made to insure orthogonality and because they had been reported to be robust to the conditions required to incorporate the α-methyl group. The synthesis of **77** involved the sequential generation of the cyclic silylene and the TBDPS ether followed by the incorporation of the C(23) methyl group.[47,48] Following its synthesis, we subjected **77** to DMDO and propenyl magnesium chloride and, to our delight, isolated β-ketoside **79** in 93% yield. This was the first time that we are aware of that a Grignard reagent had been coupled in a stereoselective fashion with an α-substituted anhydride to give the corresponding ketoside where the newly formed C–O and C–C bonds were *trans*- to one another.[49]



Scheme 11. a) $tBu_2Si(OTf)_2$, 2,6-lutidine (76%); b) TBDPSCl, imidazole (100%); c) *t*BuLi; MeI (95%); d) DMDO; propenyl magnesium chloride (93%).

As our plans to the gambierol F-ring involved an RCM reaction to a tetrasubstituted enol ether (see below) we required the incorporation of a methyl group into the allyl nucleophile. Surprising to us was that the use of our normal conditions (i.e., formation of the anhydride in CH_2Cl_2, concentration of the mixture, solvation of the resulting residue, and addition of the nucleophile) using 2-methylpropenyl magnesium chloride as the nucleophile resulted in a pinacol rearrangement and a 78% yield of ketone **81** (Table 5, entries 1–3). After considerable experimentation we found that the conditions used to generate the anhydride were important and that the use of Messegeur's "acetone free" dimethyl dioxirane was critical for success.[39] Through the use of these conditions and by avoiding the concentration of the intermediate anhydride, 2-methylpropenyl magnesium chloride could be successfully coupled with anhydride **78** to give **80** in 65% yield (Table 5, entry 4). Further optimization showed that the Grignard salt was also important; when a bromide instead of a chloride counterion was used, C-ketoside **80** was generated in 92% yield. Significant to our gambierol efforts was that the reaction was scalable (ca. 8 g), and was highly diastereoselective (>95:5).

Table 5. Addition of 2-methylpropenyl nucleophiles to anhydride **78**.

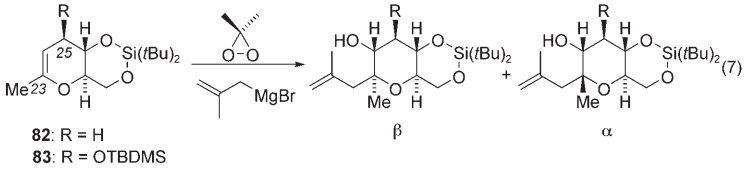


Entry	X	Conditions[a]	Additive	**80/81**	Yield [%]
1	Cl	A	none	<5:95	78
2	Cl	A	$ZnCl_2$	<5:95	78
3	Cl	A	CuI	<5:95	81
4	Cl	B	none	>95:5	65
5	Br	B	none	>95:5	92

[a] A: concentration of intermediate anhydride; residue was dissolved in THF; nucleophile added. [b] B: Messegeuer's conditions (DMDO added to the enol ether as a ca. 0.2 M solution in CH_2Cl_2); nucleophile added directly to the anhydride without concentration.

The C(25) substituent was also key to the success of the ketoside forming reaction. The use of C(25)-deoxy-substrate **82** gave a 60% yield of **84** as a 2:1 β/α mixture and C(25) TBDMS ether **83** gave **85** as a 4:1 β/α mixture in 80% yield (Table 6). Most interesting was that the mixture did not lie at the C(24) hydroxyl group but at the newly formed C(23) C–C bond. Thus, the C(25) substituent was not only influencing the oxidation reaction but, to our surprise, was also playing a role in the subsequent formation of the C(23) C–C bond. We currently believe that the reaction requires a group at C(25) group that is of sufficient size (i.e., > OTBDMS) to serve as a protecting group for the adjacent anhydride enabling it to avoid decomposition via oxocarbenium chemistry prior to formation of the C–C bond formation.[50]

Table 6. The generation of C-ketosides **84** and **85** from cyclic enol ethers **82** and **83**.



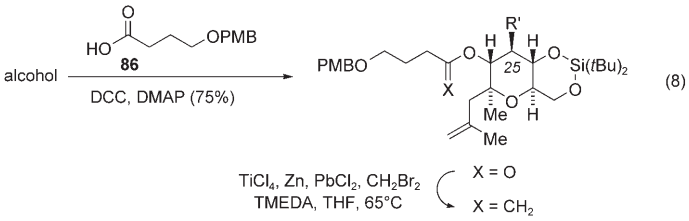
82: R = H
83: R = OTBDMS

R	β:α	Ketoside	Yield [%]
H	2:1	**84**	60
OTBDMS	4:1	**85**	80

F-Ring: Having discovered a solution to the gambierol G-ring, we next examined the aforementioned RCM chemistry to the F-ring. Not surprising was that the steric crowding about the C(24) alcohol was a significant hindrance in the conversion of **80** into the corresponding metathesis precursor. Esterification of **80** with **86** required a large excess of acid and prolonged reaction times to deliver **88** in 75% yield (Table 7, entry 1). The conversion of **88** into the corresponding acyclic enol ether using the Takai–Utimoto conditions was also sluggish, resulting in a 35% yield of **91**. Fortunately, these yields could be improved by decreasing the steric environment about the ester. For example, TMS ether **87** gave an enhanced conversion to both the ester and the acyclic enol ether (Table 7, entry 2). Ultimately, the conversion problem was solved by turning to the C(25) deoxy-substrate **84**. When subjected to the Takai–Utimoto protocol it gave an 83% yield of acyclic enol ether **93** (Table 7, entry 3).

TMS ether **89** and deoxy-substrate **90** were generated according to the sequence illustrated in Scheme 12 and Equations (9), (10), and Table 8.

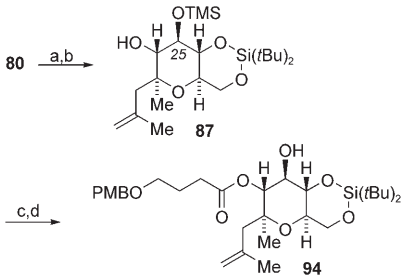
Table 7. Synthesis of the metathesis precursor.



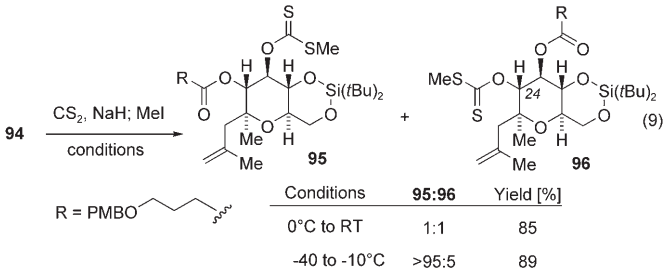
Entry	Alcohol	R′	Ester	Yield [%]	Enol ether	Yield [%]
1	**80**	OTBDPS	**88**	75	**91**	35[a]
2	**87**	OTMS	**89**	90	**92**	50[b]
3	**84**	H	**90**[c]	–	**93**	83

[a] 47% recovered **88**. [b] 33% recovered **89**. [c] For the synthesis of **90** see Scheme 12, Equations (9), (10), and Table 8.

tions (9) and (10). The most direct route to **90** (i.e., removal of the TBDPS group from ester **90** and deoxygenation) proved unworkable as it required forcing conditions that resulted in competitive removal of the silylene and/or the decomposition of **88**. Removing the TBDPS group prior to ester formation circumvented this problem. Key to the success of this route was the selective generation of a C(25) TMS ether to give **87**. Incorporation of the ester was followed by TMS ether hydrolysis to give alcohol **94**.



Scheme 12. a) NaH, HMPA (92%); b) TMSOTf, *i*Pr$_2$NEt (90%); c) **86**, DCC, DMAP (90%); d) HOAc, H$_2$O (98%).



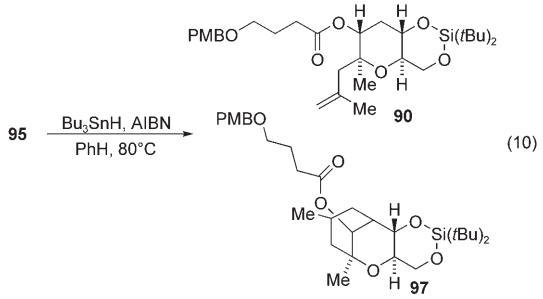
The Barton–McCombie protocol was used to deoxygenate **94** [Eqs. (9) and (10)]. In the initial xanthate formation, the reaction temperature was critical; elevated temperatures resulted in a substantial quantity of **96** from ester migration and C(24) xanthate formation.

Deoxygenation of **95** using free-radical conditions (Bu_3SnH/AIBN, 80°C) gave **90** [Eq. (10)]. Not surprisingly, this reaction was sensitive to concentration. If run at relatively high concentration (0.125 M), the desired product was generated in 90% yield (Table 8). At lower concentrations tricycle **97** from a 6-*endo* cyclization of the intermediate radical became the dominant, or when concentrations were low enough, the only isolated product.[51]

With acyclic enol ethers **91** and **93** in hand (Table 7), we examined their conversion into the corresponding F-ring enol ether using RCM. In light of the fact that the F-ring required the generation of a tetrasubstituted enol ether it was not surprising that these reactions were sluggish. The use of **91** and either the Schrock Mo alkylidene catalyst **39** at 65°C or the Grubbs II catalyst **38** at RT resulted in the complete recovery of starting material (Table 9, entries 1–3). The stability of the Grubbs catalyst at elevated temperatures turned out to be critical.[52] When **91** was subjected to **38** (45 mol%, added in three portions) at 65°C a small amount (ca. 5%) of tetrasubstituted enol ether **98** was isolated (Table 9, entry 4). When the temperature of the reaction of **91** or **93** was increased to 80°C we isolated **98** or **99** in 82 and 83% yield, respectively (Table 9, entries 5 and 6).

In contrast to the enol ether RCM reactions of the substrates that have been described previously in this manuscript, we believe that the reactions of the more sterically encumbered olefinic substrates **91** and **93** proceed through less reactive Fischer carbene intermediates (i.e., **100**, **101**), thus the need for elevated temperatures [Eq. (12)].[53]

Table 8. Deoxygenation of xanthate **95**.



c [M]	**90**/**97**[a]	Yield [%]
0.003	<5:95	50
0.014	1:1.4	60
0.125	>95:5	90

[a] **97** was isolated as a 3:1 mixture of diastereomers.

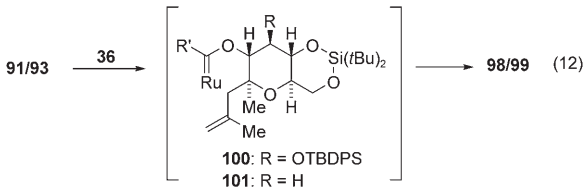
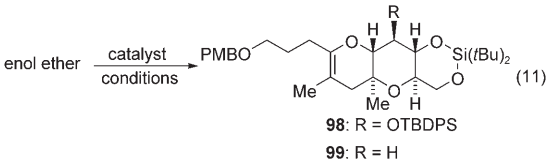


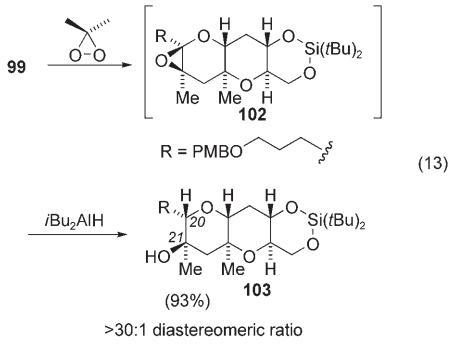
Table 9. Generation of tetrasubstituted enol ethers **98** and **99** using RCM.



Entry	Enol ether	R	Catalyst (mol%)	Conditions	Yield [%]
1	**91**	OTBDPS	**39** (20)	hexanes, 65°C	0
2	**91**	OTBDPS	**38** (20)	PhH, RT	0
3	**93**	H	**38** (20)	PhH, RT	0
4	**91**	OTBDPS	**38** (45)[a]	PhH, 65°C	5
5	**91**	OTBDPS	**38** (45)[a]	PhH, 80°C	82
6	**93**	H	**38** (45)[a]	PhH, 80°C	83

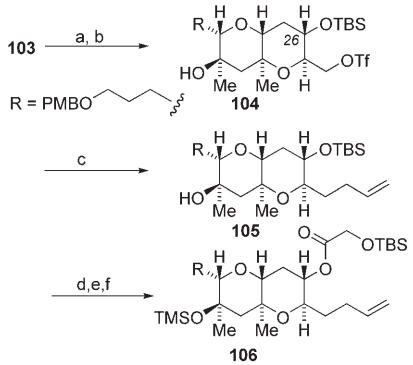
[a] **38** was added over three additions (15% + 15% + 15%).

Remaining to the F-ring were the C(20) and C(21) stereocenters. From tricyclic enol ether **99**, DMDO oxidation and DIBAL-H reduction of the intermediate anhydride **102** provided the requisite stereocenters and **103** in a highly efficient fashion [Eq. (13)]. As discussed previously, we believe that the generation of the C(20) stereocenter comes from a directed reduction [see Eq. (5)].



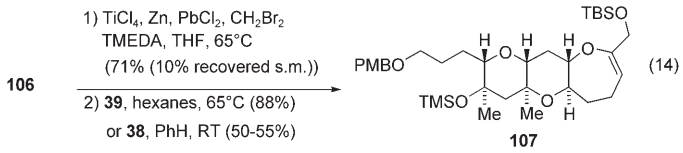
(13)

H-Ring: Having completed the F-ring, we moved to the seven-membered H-ring. In addition to the challenge of employing enol ether–olefin RCM to generate the seven-membered ring we were also concerned with control of the C(30) and C(31) stereocenters. To examine this, the cyclic silylene was removed using HF·pyridine and the resulting triol was transformed into the primary triflate and secondary TBS ether to give **104** (Scheme 13). Coupling with propenyl cuprate delivered **105**.[54] Removal of the TBS group, esterification, and C(21) TMS ether formation gave olefinic-ester **106**.



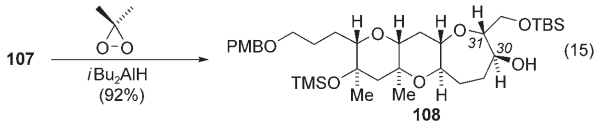
Scheme 13. a) HF·pyridine, THF, 0°C (100%); b) Tf_2O, 2,6-lutidine, CH_2Cl_2, −65°C; TBSOTf, 2,6-lutidine, 0°C (79%); c) propenyl magnesium chloride, CuI, Et_2O, −40°C → RT (88%); d) TBAF, THF (85%); e) $TBSOCH_2CO_2H$, DCC, DMAP, (95%); f) TMSCl, DMAP, Hünigs base (100%).

We were pleased to find that **106** was amenable to RCM [Eq. (14)]. Sequential exposure of **106** to the Takai–Utimoto conditions and Schrock's molybdenum catalyst **39** resulted in a 62% yield of **107** over the two steps (10% recovered starting material). In contrast to our previous use of RCM to generate oxepenes,[16] the Grubbs II catalyst **38** was less successful than the Schrock catalyst, its use resulted in the generation of **107** in 35–39% overall yield from **106**.



(14)

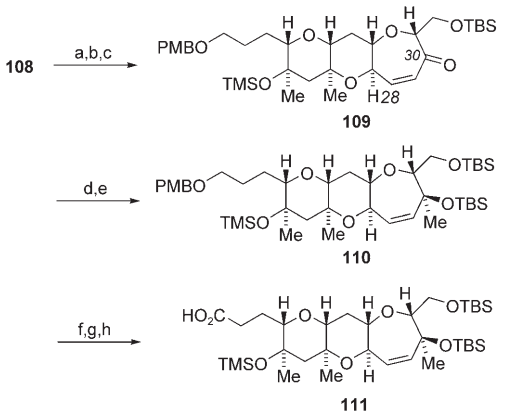
With the H-ring skeleton in place, we were now prepared to examine the formation of the C(30) and C(31) stereocenters. To our delight the use of the DMDO oxidation, DIBAL-H reduction sequence resulted in the generation of **108** in 92% yield as a single diastereomer [Eq. (15)]. From the analysis of a calculated transition state structure of the DMDO oxidation on a substrate related to **107**, we tentatively believe that an unfavorable torsional interaction between the allylic axial hydrogen in **107** and DMDO results in the observed facial selectivity.[55]



(15)

To complete the F–H substrate, it remained to introduce the C(28)−C(29) alkene and the C(30) tertiary alcohol. To this end, TPAP and Saegusa oxidations resulted in the incorporation of the requisite enone as **109** (Scheme 14). Borrowing from Yamamoto and Kadota's work, addition of methyl magnesium bromide gave tertiary ether **110** following silyl ether formation.[56] The stereoselectivity in this transformation is interesting; we believe that axial attack of methyl magnesium bromide is dictated by developing eclipsing interactions between the C−O bond and the adjacent C(30) silyloxymethyl substituent during the transition state that would lead to the undesired axial alcohol.[57] The completion of the synthesis of the F–H coupling precursor **111** involved oxidative hydrolysis of the PMB group, TPAP oxidation of the resulting primary alcohol, and sodium chlorite oxidation to the corresponding carboxylic acid.

To summarize our generation of gambierol's A–C and F–H ring systems, we have demonstrated the versatility of the glycosyl anhydride, enol ether–olefin RCM strategy to fused polycyclic ethers. These efforts have directed us to an interesting substituent and reagent influence on the generation of C-ketosides from the corresponding anhydrides. Also interesting is a novel Claisen rearrangement reaction to a bicyclic C-ketoside that is controlled by subtle conformational issues. In the area of enol ether–olefin RCM chemistry, we have been able to generate a tetrasubstituted enol ether and



Scheme 14. a) TPAP, NMO (90%); b) LiHMDS, NEt_3, TMSCl; c) Pd$(OAc)_2$, CH_3CN, RT (90%, 2 steps); d) MeMgBr, −70°C (94%); e) TBSOTf, CH_2Cl_2, RT (96%); f) DDQ, CH_2Cl_2, H_2O (98%); g) TPAP, NMO, CH_2Cl_2; h) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, H_2O, *t*BuOH (90%, 2 steps).

a highly substituted oxepene using either the second generation Grubbs catalyst **38** or the Schrock catalyst **39**. Equally important to these fundamental issues is that the reactions listed above have enabled us to generate sufficient quantities of the A–C and F–H substrates to complete our gambierol efforts. This work is described in the accompanying manuscript.

Acknowledgements

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