

Total Synthesis of Gambierol: Subunit Coupling and Completion

Henry W. B. Johnson, Utpal Majumder, and Jon D. Rainier*^[a]

Abstract: The preceding manuscript detailed our synthesis of the gambierol A–C and F–H ring precursors. Reported herein is a description of the coupling of the two precursors and the conversion of the coupled material into gambierol. Coupling of the subunits involved ester formation, enol ether RCM, and mixed thioketal formation

and reduction. By employing this strategy we were able to bring highly advanced subunits into the coupling and, as a result, we were able to minimize

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the number of post-coupling transformations required to complete gambierol. At the completion of the synthesis, we generated 7.5 mg (1.5% overall yield) of (–)-gambierol in 44 steps (longest linear sequence).

Introduction

As mentioned in the preceding manuscript, gambierol is a member of the marine ladder toxin family and was isolated by Yasumoto and co-workers from cultured *Gambierdiscus toxicus* (GI-1 strain).^[1,2] As it is not available in any significant quantities from the natural source,^[3] synthesis is probably the most effective method to uncover its biological properties and the only way to carry out SAR work.^[4] When we became interested in the chemical synthesis of gambierol we had two criteria that we considered: First, any approach to its synthesis needed to be efficient enough to enable us to carry out structure activity work to gain better insight into gambierol's biological target(s). Equally critical to us was that the approach employ novel coupling chemistry that once developed might prove to be beneficial for future work in the ladder toxin/polyether area. With this in mind, we opted to pursue an approach that would utilize enol ether–olefin ring-closing metathesis (RCM) chemistry in subunit coupling that would result in the generation of the D-ring.^[5] If successful, this would set the stage for well-precedented ketal reduction chemistry to the E-ring.^[6] Subsequently, in-

corporation of the H-ring side chain would result in the synthesis of gambierol.

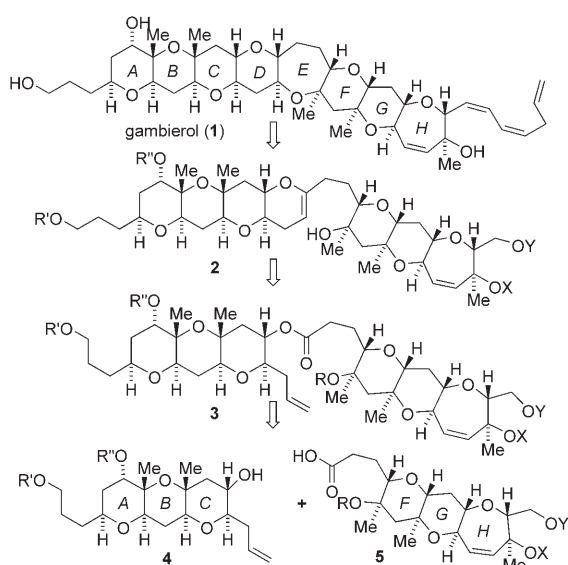
Results and Discussion

From our perspective, the strategy outlined above was advantageous in that: a) esterification would be employed to couple the two subunits (i.e., **4** + **5** → **3**); b) the enol ether–olefin RCM chemistry would be used to generate the presumably easier to form six-membered D-ring (**3** → **2**); c) the more difficult seven-membered E-ring would come from a cyclization and ketal reduction sequence (**2** → **1**); d) in principle, the H-ring olefin would be compatible with this strategy and thus reduce the number of post-coupling transformations. The preceding manuscript detailed our synthesis of the gambierol A–C and F–H ring precursors (Scheme 1).^[7] Reported herein is a description of the coupling of the two precursors and the conversion of the coupled material into gambierol.

Subunit coupling—1st Generation strategy: Our efforts to couple the A–C and F–H precursors began with the generation of **8** from the esterification of **7** with **6**. A two-step enol ether–olefin RCM reaction using the Grubbs II catalyst to effect ring-closure was used to generate dihydropyran **10** (Scheme 2).^[8] Oxidation of the cyclic enol ether by using dimethyl dioxirane (DMDO) and directed reduction using DIBAL-H provided the corresponding secondary alcohol as a 3:1 mixture of diastereomers.^[8] Of note is that the use of hydroboration, oxidation on **10** resulted in the competitive

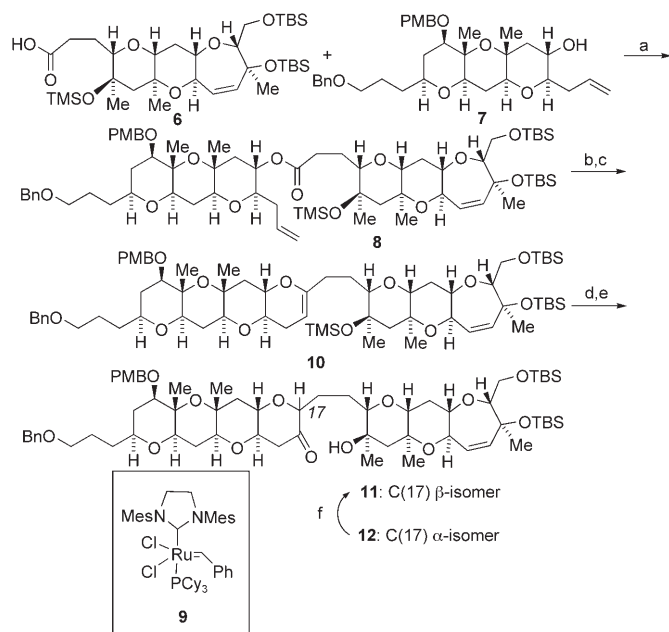
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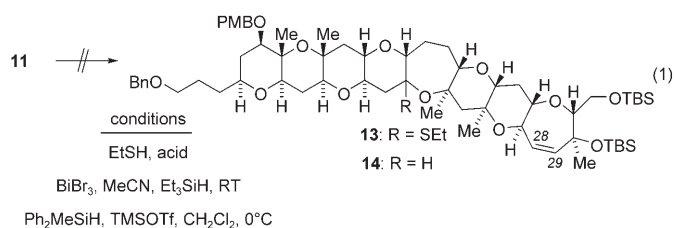
Scheme 1.

reduction of the H-ring olefin.^[9] That the reaction gave a mixture of C(17) diastereomers favoring the undesired α -isomer was not a problem; we took advantage of the thermodynamic stability of the desired C(17) β -stereochemistry by oxidizing the C(16) alcohol and equilibrating the C(17) stereocenter to give **11**.^[10] Equilibration resulted in a 4:1 mixture of isomers that could be separated and recycled.

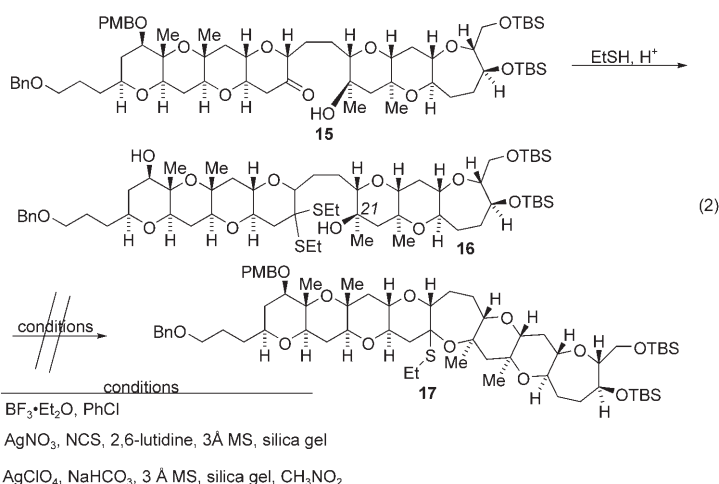


Scheme 2. a) DCC, DMAP, CH_2Cl_2 , RT (90%); b) TiCl_4 , TMEDA, THF, CH_2Cl_2 , Zn, PbCl_2 , CH_2Br_2 ; c) **9** (20 mol%) (75%, two steps); d) DMDO (acetone free), CH_2Cl_2 , -65°C to RT; DIBAL-H, -65°C (80%, 3:1 α/β mixture); e) TPAP, NMO (80%); f) DBU, PhH, 80°C (100%, β/α 4:1); TMEDA: tetramethylethylenediamine, TPAP: tetrapropylammonium perruthenate.

With **11** in hand, it remained to form the E-ring. Unfortunately, all attempts to affect the cyclization of **11** were unsuccessful [Eq. (1)]. Included were attempts to generate the corresponding mixed thioketal through the use of EtSH and various acids and the generation of the cyclic ether directly through the use of BiBr_3 and Et_3SiH or TMSOTf and Ph_2MeSiH .^[11,12] Based upon the lack of olefinic protons in the ^1H NMR spectra of recovered samples we believe that the H-ring olefin was undergoing competitive decomposition under the reaction conditions.

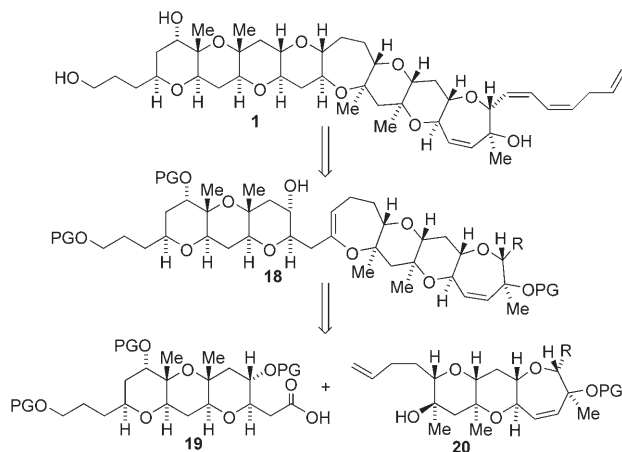


In an attempt to avoid the olefin decomposition problem, we examined the corresponding C(28)–C(29) saturated substrate. Although somewhat less than ideal in that the use of this substrate would require that the olefin be introduced post-coupling, at the very least these experiments would enable us to determine the overall feasibility of the approach. With this in mind, coupling, metathesis, and oxidation/reduction was carried out as described previously to give **15** [Eq. (2)].^[13] Subjecting **15** to a variety of conditions to generate the corresponding O,S-ketal all failed.^[14] The main products were either the acyclic dithiane **16** or decomposition when attempts were made to push the reaction.



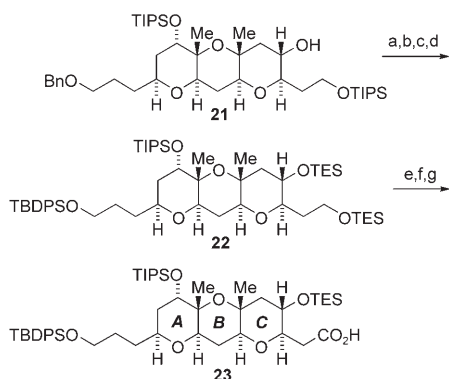
From the efforts described above, it was clear that an alternate coupling protocol was needed. Because of our continued belief that it could become a highly efficient means of generating polycyclic ethers, we opted to continue to

pursue an enol ether–olefin RCM strategy (Scheme 3). However, instead of employing metathesis to generate the “easier” D-ring, we would use it to generate the seven-membered E-ring. Subsequently, a ketal cyclization and reduction sequence would be employed to generate the D-ring.



Scheme 3.

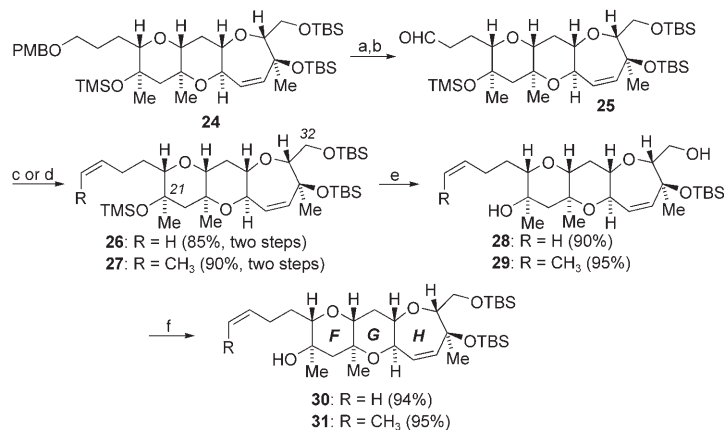
To examine this approach, our syntheses of both the A–C and F–H subunits required modification. The generation of the A–C substrate **23** was carried out from **21** according to the sequence of reactions illustrated in Scheme 4. Exchange of the C(1) benzyl ether for a TBDPS ether and selective acid catalyzed hydrolysis of the primary TIPS ether in the presence of the secondary TIPS ether and primary TBDPS ether gave **22** after bis-TES ether formation. Selective hydrolysis of the primary TES ether and oxidation provided coupled precursor **23**.



Scheme 4. a) LiDBB, THF, -78 to -40 °C (80%); b) TBDPSCl, NEt_3 , DMAP, CH_2Cl_2 , -78 °C (95%); c) CSA, CH_2Cl_2 , RT (92%); d) TESCl, NEt_3 , DMAP, CH_2Cl_2 (100%); e) AcOH, $\text{H}_2\text{O}/\text{MeOH}$ (97%); f) TPAP, NMO, CH_2Cl_2 (97%); g) NaClO_2 , 2-methyl-2-butene, NaHPO_4 , H_2O , *t*BuOH (95%); LiDBB: lithium 4,4'-di-*tert*-butylbiphenylide, CSA: camphorsulfonic acid.

The gambierol F–H precursors **30** and **31** were constructed according to the sequence illustrated in Scheme 5. Oxidative hydrolysis of the PMB group was followed by TPAP ox-

idation of the resulting primary alcohol. For reasons that will become clear (see below), we utilized both the terminal and the internal olefin containing substrates **26** and **27**, respectively, as precursors to the E-ring. Subsequent to olefin formation, hydrolysis of the C(21) tertiary TMS ether also resulted in the hydrolysis of the C(32) TBS ether. Reincorporation of the TBS ether gave coupling precursors **30** and **31**.



Scheme 5. a) DDQ, H_2O , CH_2Cl_2 (98%); b) TPAP, NMO; c) PPh_3PCH_2 ; d) $\text{Ph}_3\text{PCHCH}_3$; e) CSA, MeOH; f) TBSCl, NEt_3 , DMAP, CH_2Cl_2 ; DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

With the precursors in hand, we examined their unification [Table 1, Eq. (3)]. Not surprising based upon our earlier work that attempted to use it to generate an E-ring ketal, esterification of the C(21) tertiary alcohols **30** and **31** with acids **23** or **32**^[15] proved challenging. After considerable experimentation,^[16] we found that the Yamaguchi protocol worked the best in our hands.^[17] Important was that we employ elevated temperatures and, because the intermediate anhydride was not stable for indefinite periods of time, that the formation of the anhydride be monitored by ^1H NMR.^[18] When this protocol was followed, the coupled products **33** and **34** could be generated in $\geq 90\%$ yield (Table 1, entries 8 and 9).

We were now prepared to examine the metathesis chemistry to the E-ring. To this goal, our attempts to generate the acyclic enol ether corresponding to ester **33** were completely ineffective. Instead, we isolated a very small amount of cyclic enol ether **37** along with a mixture of products all lacking the terminal olefin [Eq. (4)].

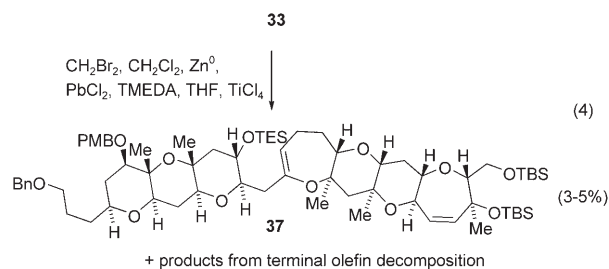
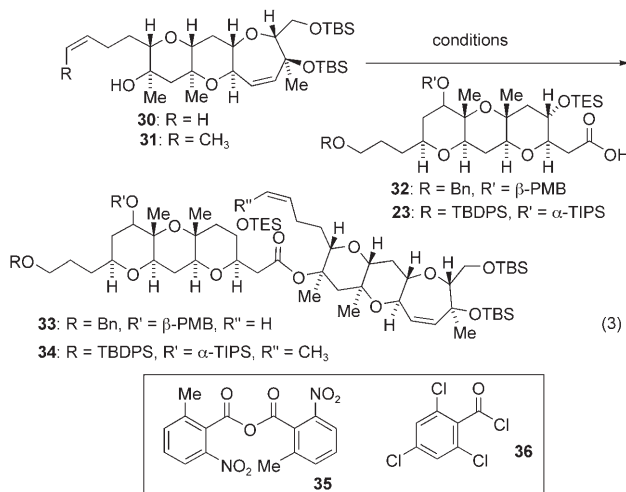


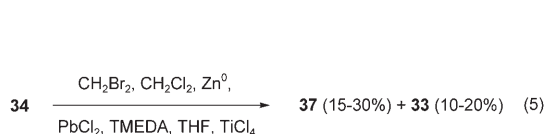
Table 1. Subunit coupling of gambierol A–C precursors **32** and **23** with F–H precursors **30** and **31**.



Entry	Alcohol	Acid	Conditions	R	R'	R''	Ester	Yield [%]
1	30	32	DCC, DMAP	Bn	β -PMB	H	33	0
2	30	32	(COCl) ₂ ; NaH	Bn	β -PMB	H	33	0
3	30	32	(COCl) ₂ ; Zn	Bn	β -PMB	H	33	0
4	30	32	35	Bn	β -PMB	H	33	0
5	30	32	A, ^[a] 12 h	Bn	β -PMB	H	33	30–60
6	30	32	B, ^[a] 0.5 h	Bn	β -PMB	H	33	35
7	30	32	B, ^[a] 4 h	Bn	β -PMB	H	33	0
8	30	32	B, ^[a] 1.3 h	Bn	β -PMB	H	33	92 ^[b]
9	31	23	B, ^[a] 1.3 h	TBDPS	α -TIPS	CH ₃	34	90 ^[b]

[a] Condition A: **36** (6 equiv), NEt₃ (7.5 equiv), DMAP (7.5 equiv), CH₂Cl₂ (–20 to –5 °C); condition B: **36** (6 equiv), NEt₃ (7.5 equiv), DMAP (7.5 equiv), CH₂Cl₂ (40 °C). [b] Progress of anhydride formation was monitored by ¹H NMR.

In light of the steric environment about the ester in **33**, it was not surprising that acyclic enol ether formation was problematic.^[19,20] We decided to simultaneously increase the stability of the olefin and our chances of generating the acyclic enol ether by utilizing internal alkene substrate **34**. Interestingly however, when **34** was subjected to the Takai–Utimoto protocol preferential decomposition of the olefin was again observed. The only identifiable products from this transformation were cyclic enol ether **37** and terminal olefin **33**.

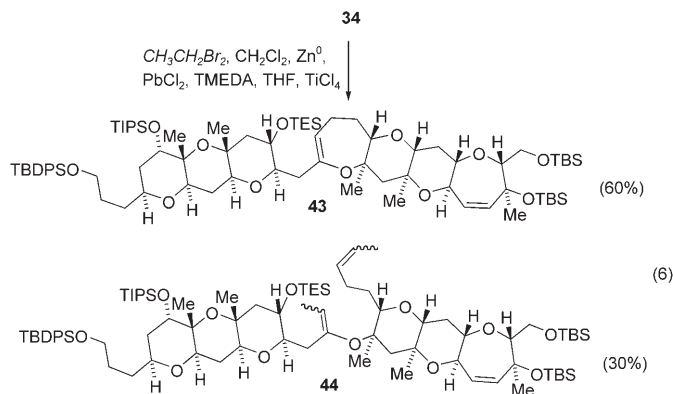


At this stage, we decided to attempt to optimize the formation of cyclic enol ether **37** by taking advantage of the propensity for the reaction of the presumed Ti methylidene from the Takai–Utimoto reagent with the olefin.^[21,22] Mechanistically, the interaction of the Ti methylidene with the alkene in **34** produces one of two intermediate titanacyclobutanes (Scheme 6). The intermediate that leads to cyclic enol ether **37** has Ti oriented at the more hindered, “internal” position of the alkene (i.e., **38**). The alternative “undesired” orientation proceeds through titanacyclobutane **40** having Ti proximal to the methyl group and leads to termi-

nal olefin **33**. Based upon the poor conversions observed when **33** was independently subjected to the reaction conditions [Eq. (4)], we believe that the reasons for the low and capricious conversions in the reaction was related to the instability of terminal olefin **33** to the reaction conditions; it was being siphoned out of the metathesis pathway by undergoing a competitive non-productive decomposition. To overcome this and to improve the overall efficiency of this process, we proposed to employ a Ti alkylidene (R ≠ H) rather than a methylidene (R=H). Reaction of an alkylidene in the “undesired direction” would simply result in the re-generation of the relatively stable substituted olefin (i.e., **34**). Ultimately the alkylidene would react to give **38** and cyclic product **37** after its decomposition to **39** and cyclization. From a practical perspective, critical to this proposal was that the Takai–Utimoto protocol has been shown to be

amenable to the generation of a variety of alkylidenes through the use of different dibromoalkanes in its in situ preparation.^[23]

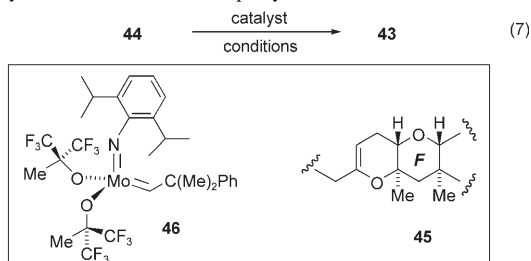
We were very pleased when this hypothesis proved to be accurate. By subjecting α -TIPS substrate **34** to the Takai–Utimoto ethylidene reagent that was generated from dibromoethane instead of dibromomethane we isolated **43** in 60% yield. Interesting is that this reaction also led to a substantial quantity of acyclic enol ether **44** [Eq. (6)].



Acyclic enol ether **44** could be converted into cyclic substrate **43** when subjected to the 2nd generation Grubbs catalyst but only when ethylene was added to the reaction. It

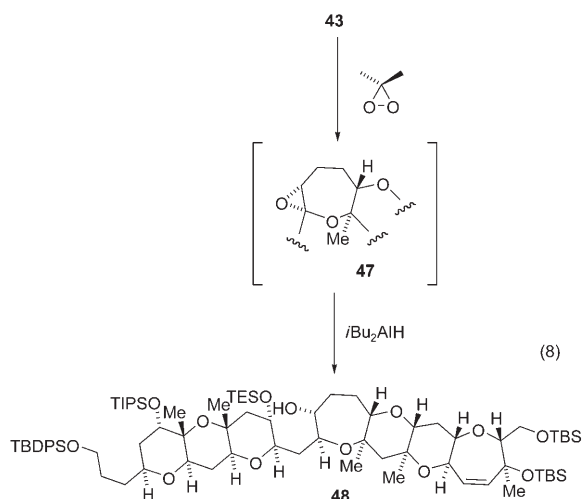
was important that **44** be converted into the corresponding terminal olefin prior to it undergoing cyclization.^[24] Elevated reaction temperatures were required to avoid the generation of dihydropyran **45** from isomerization of the olefin and cyclization. With the ability to transform **44** into **43**, our overall yield for the conversion of ester **34** into heptacycle **43** increased to a respectable 80% (Table 2).

Table 2. Conversion of acyclic enol ether **44** into heptacycle **43**.



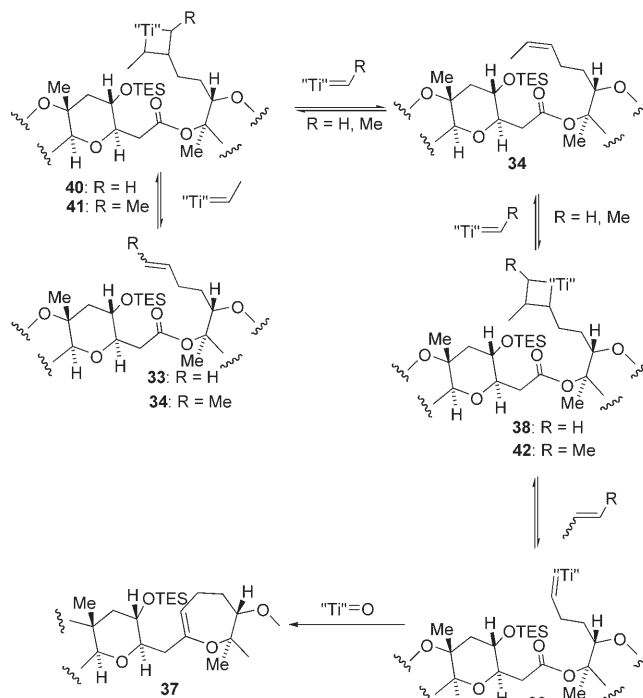
Entry	Conditions	Yield [%] (43)
1	9 (20 mol%), PhH, RT to 80°C	0 (60% recovered 44)
2	9 (20 mol%), PhCH ₃ , 110°C	0 (60% 45)
3	46 (20 mol%), hexanes, 60°C	0 (80% recovered 44)
4	9 (20 mol%), PhH, 80°C, ethylene (1 atm); N ₂ purge, 9 (20 mol%), 40°C	30 (40% 45)
5	9 (20 mol%), PhH, 80°C, ethylene (1 atm); N ₂ purge, 9 (20 mol%), 80°C	65 (20% 45)

D-Ring: With the E-ring finally in hand, we turned our attention to the reductive cyclization chemistry to the D-ring. To this goal, selective oxidation of the cyclic enol ether with DMDO followed by reduction of the intermediate epoxide with DIBAL-H gave secondary alcohol **48** as a 10:1 mixture of diastereomers [Eq. (8)]. We did not anticipate the facial selectivity in the dioxirane reaction as it is from the side of the C(21) angular methyl group. This phenomenon seems to be a general feature of fused oxepenes having α -substitution as evidenced by our results with the gambierol H-ring and with bicyclic models from tribenzyl-D-glucal.^[25,26]



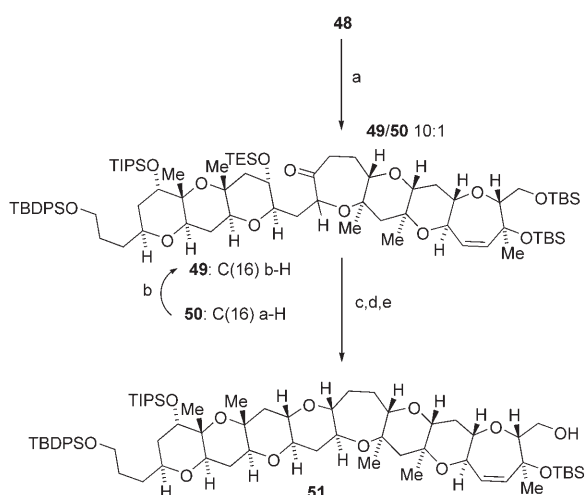
Oxidation of the secondary alcohol using TPAP gave ketones **49** and **50** as a 10:1 mixture of diastereomers

(Scheme 7). The isomers were separated and the minor isomer (e.g. **50**) was recycled to a 4:1 mixture of isomers by using imidazole and heat. Other bases (DBU) were much less effective in this reaction.^[10] Following its formation, ketone **49** was treated with CSA to remove the C(13) TES group. As was seen previously in our synthesis of the F–H coupling precursor (see Scheme 6), it was fortuitous that these conditions also removed the C(32) TBS group. Gambierol's octacyclic core was completed by subjecting the hydroxy ketone from **49** to Zn-(OTf)₂ and EtSH. In contrast to our attempts to generate the E-ring, this reaction generated a single O,S-ketal diastereomer without any degradation of the H-ring olefin. Undoubtedly, the more facile cyclization to form the D-ring is responsible for this result. Reduction of the O,S-ketal by using Ph₃SnH then gave the gambierol octacycle in 97% yield.



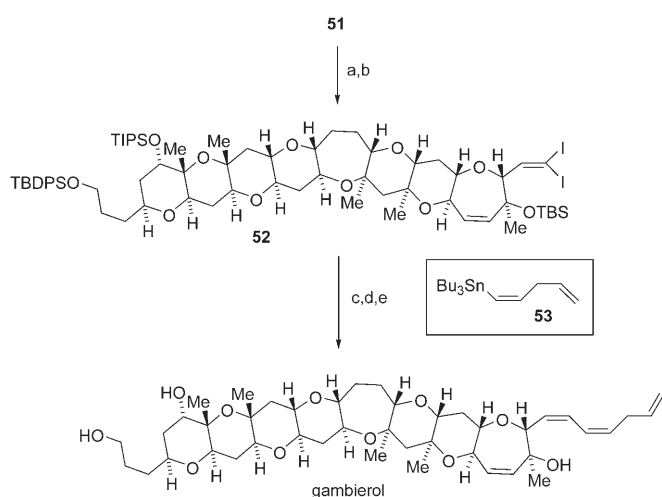
Scheme 6.

It remained to attach the skipped triene side chain and remove the remaining protecting groups. To this end, we borrowed heavily from the work of Yamamoto and Sasaki.^[2,27] Oxidation of the primary alcohol was followed by the conversion of the resulting aldehyde into the corre-



Scheme 7. a) TPAP, NMO (93%); b) imidazole, CH_2Cl_2 , 40 °C (100%, β/α 4:1); c) CSA, MeOH (90%); d) $\text{Zn}(\text{OTf})_2$, EtSH (86%); e) Ph_3SnH , AIBN (97%).

sponding diiodoalkene using a modified Corey–Fuchs addition reaction (Scheme 8).^[28] Stereoselective reduction using $\text{Zn}(\text{Cu})$ couple,^[29] global deprotection using SiF_4 ,^[30] and Stille coupling of the resulting triol with dienyln stannane **53**^[27] provided (–)-gambierol. The spectroscopic and physical data for synthetic gambierol was identical to that reported previously. Impressive in this work is that only 12 post-coupling transformations were required to complete the synthesis from A–C and F–H subunits **23** and **31**, respectively. Overall, our synthesis involved 44 steps (longest linear sequence from D-glucal, 69 total steps) and resulted in a 1.5% overall yield of gambierol.^[31] Using the chemistry described we were able to generate 7.5 mg of gambierol that we are currently using in ion channel binding studies.



Scheme 8. a) TPAP, NMO (100%); b) CH_3I , KOtBu , PPh_3 (94%); c) Zn/Cu couple; d) SiF_4 (95%); e) $[\text{Pd}_2(\text{dba})_3]$, $\text{P}(\text{furyl})_3$, CuI , DMSO, **53** (85%).

To conclude, this manuscript has described our total synthesis of the marine ladder toxin gambierol. This work has described a new subunit coupling strategy to polycyclic ethers. Critical to the success was the use of a titanium ethylidene in an olefin metathesis, carbonyl–olefination cyclization reaction. Current investigations include the exploration of the biological properties of synthetic gambierol and analogues as well as the application of this coupling strategy to other marine polycyclic ethers.

Acknowledgements

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