

Synthesis of an F–H Gambierol Subunit Using a C-Glycoside-Centered Strategy

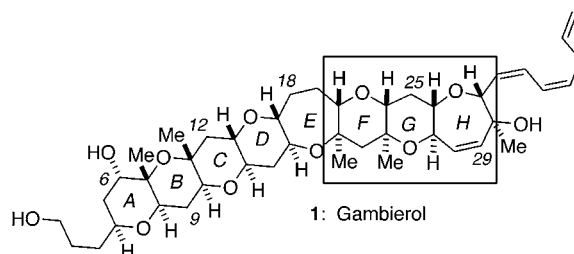
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ABSTRACT



This manuscript describes our synthesis of the F–H subunit of gambierol. In addition to the synthesis of the tricycle, of note is an interesting protecting group influence on the generation of a C(23) C-glycoside as well as the use of ring-closing metathesis to generate a tetrasubstituted enol ether.

Gambierol, a member of the marine ladder toxin family of natural products, was isolated in 1993 by Yasumoto and co-workers from the marine dinoflagellate *Gambierdiscus toxicus*.¹ As part of this initial work, the Yasumoto group determined gambierol's relative configuration; they subsequently elucidated its absolute structure.² Not surprisingly, gambierol's polycyclic ether architecture and intriguing biological activity has attracted the attention of chemists interested in its synthesis. To date, this has led to a number of important studies³ and the total synthesis of gambierol by the Sasaki and Yamamoto groups.⁴

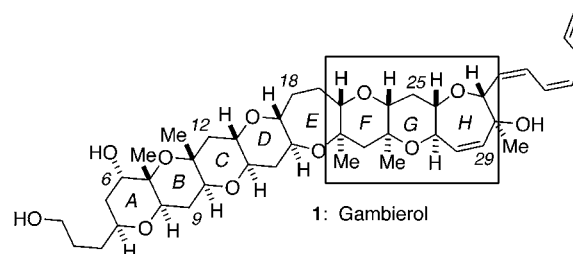


Figure 1.

Our interest in gambierol stems from our program that targets the chemical synthesis of polycyclic ether-containing natural products. Central to our approach has been the generation of carbon C-glycosides from the single flask coupling of glycol anhydrides with carbon nucleophiles.^{5–7} As applied to gambierol, we recently described the use of

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(1) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361.

(2) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *40*, 97.

(3) (a) Marmsater, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144. (b) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6702. (c) Marmsater, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027. (d) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 3562. (e) Sasaki, M.; Tsukano, Tachibana, K. *Org. Lett.* **2002**, *4*, 1747.

(4) (a) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983. (b) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46.

(5) For a recent monograph on C-glycoside synthesis, see: Postema, M. H. D. In *Glycochemistry Principles, Synthesis and Applications*; Bertozzi, C., Wang, P. G., Eds.; Marcel Dekker: New York, 2000; pp 77–131.

this strategy to synthesize the A–D subunit.⁸ Outlined herein is the synthesis of the F–H subunit.

Our approach to the F–H subunit was to utilize differentially protected glucal as the G-ring, introduce the F-ring using a *C*-glycoside-forming reaction, and then to pursue the synthesis of the H-ring. Although glucal contains an additional hydroxyl substituent (C(25) in gambierol), we believed that the additional functionality would be beneficial in that it would direct the facial selectivity in the epoxidation reaction and ultimately the formation of the C(24) and C(23) stereocenters.

With this plan in mind, our synthesis of the F–H subunit began with D-glucal derivative **2**.⁹ Introduction of the C(23) methyl group (gambierol numbering system) gave *C*-glycoside precursor **3**.¹⁰ To determine the feasibility of the oxidation/coupling sequence, we examined the reaction of the epoxide from glycal **3** with a number of nucleophiles (Table 1). To our immense pleasure, the epoxidation of **3**

Table 1.

entry	nucleophile	R	C-glycoside	yield	4:5
1			4a	90%	>95:5 ^a
2			4b	91%	>95:5 ^a
3			5	50%	<5:95 ^a
4			4c	90%	>95:5 ^a

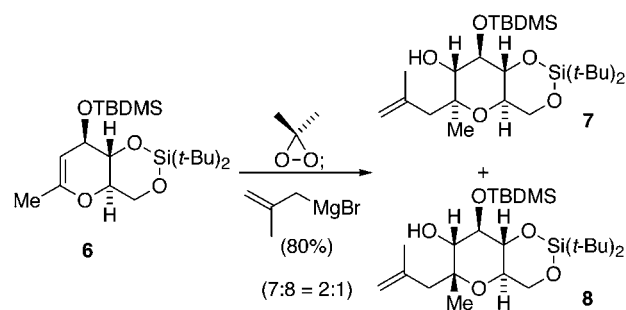
^a Minor product was not observed by ¹H NMR.

with dimethyl dioxirane (DMDO)^{11,12} followed by the addition of propenylmagnesium chloride or propynylmag-

nesium chloride gave *C*-glycosides **4a** or **4b**, respectively, as single diastereomers in high yield.^{13,14}

To generate the gambierol skeleton, methyl substitution on the nucleophile was required; unfortunately, all attempts at coupling the epoxide from **3** with 2-methylpropenylmagnesium chloride were unsuccessful and led to pinacol rearrangement product **5** (entry 3). As we had previously found that the success of some glycal anhydride coupling reactions was highly dependent on the nature of the counterion on the nucleophile,^{6c} we examined the reaction of 2-methylpropenylmagnesium bromide with the epoxide from **3**. We were extremely pleased to find that this coupling was successful to give **4c** in 90% yield.

Having achieved the synthesis of the desired *C*-glycoside, we had the opportunity to examine the influence of C(25) substitution on the coupling reaction. Unexpectedly, the *tert*-butyldiphenylsilyl (TBDPS) group proved to be important not only in the DMDO oxidation but also for the subsequent C–C bond-forming sequence. That is, when TBDPS was replaced by *tert*-butyldimethylsilyl (TBDMS), the selectivity in the coupling diminished significantly (eq 1). While the nature of the TBDPS effect is presently unclear to us, we do not believe that it can be simply attributed to steric interactions, as the TBDPS group sits on the face of the epoxide that undergoes attack.



With an efficient route to *C*-glycoside **4c** in hand, our next challenge was the generation of the tetrasubstituted enol ether required for the synthesis of the F-ring. From the outset, our plan had been to use an enol ether–olefin ring-closing metathesis (RCM) reaction. This was clearly a daunting task; while a number of related transformations have taken place,¹⁵ to the best of our knowledge, there was very little precedent

(6) (a) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. (b) Rainier, Cox, J. M. *Org. Lett.* **2000**, *2*, 2707. (c) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997.

(7) Among the more challenging structural features of gambierol are the C(7), C(11), C(21), and C(23) stereocenters. These centers contain angular methyl groups oriented in a 1,3-disposition to one another and, for our approach, require the addition of a carbon nucleophile to the more substituted end of a trisubstituted glycal anhydride. For synthetic work by others toward these centers, see refs 3 and 4 and: Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8653.

(8) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919.

(9) Parker, K. A.; Georges, A. T. *Org. Lett.* **2000**, *2*, 497.

(10) Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sinay, P. *Tetrahedron Lett.* **1986**, *27*, 6201.

(11) For the preparation of DMDO, see: Adam, W.; Bialas, J.; Hadjirapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

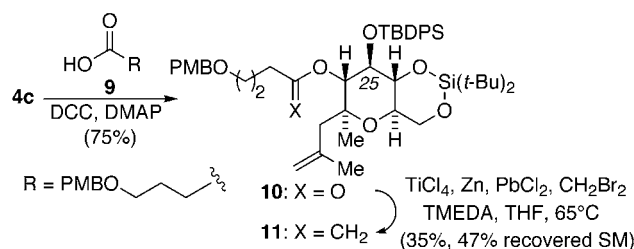
(12) To obtain reproducible yields on a large scale, we used Messeguer's "acetone-free" conditions. The use of this protocol allowed us to avoid the concentration of the epoxide. See the Experimental Section and: Ferrer, M.; Gibert, M.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron Lett.* **1996**, *37*, 3585.

(13) Our previous work with similarly substituted epoxides had resulted in poor diastereoselectivity and/or low yields. The major products from these reactions were generally rationalized as coming from the formation of intermediate oxocarbenium ions. See refs 6 and 8.

(14) We have also coupled Al nucleophiles with trisubstituted glycal anhydrides. See refs 6b and 6c.

(15) For selected examples of enol ether–olefin RCM, see: (a) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029. (b) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123. (c) Postema, M. H. D. *J. Org. Chem.* **1999**, *64*, 1770. (d) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372. (e) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (f) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179.

for the formation of a tetrasubstituted enol ether.¹⁶ With this in mind, **4c** was converted into RCM precursor **11**. Esterification of the C(24) hydroxyl group required a large excess of acid **9**, DCC, and DMAP for success. The subsequent enol ether-forming reaction using the Takai protocol¹⁷ was even more problematic; despite considerable effort, we were able to generate enol ether **11** in only 35% yield.¹⁸ In light of the steric crowding about C(24) in **4c**, it is probably not surprising that these conversions gave us difficulty.



With **11** in hand, we investigated the generation of the F-ring using ring-closing metathesis (RCM). Because of its generally higher reactivity, we initially examined Schrock catalyst **13**;¹⁹ to our disappointment, we only recovered starting material when **11** was subjected to **13** (Table 2, entry

Table 2.

Reaction scheme showing the RCM of **11** to **12** using catalyst **13**. **11** reacts with catalyst **13** under conditions to form **12**. R = OPMB.

entry	catalyst	conditions	yield
1	13	hexanes, 65°C	0%
2	14	PhH, rt	0%
3	14	PhH, 65°C	5%
4	14	PhH, 80°C	82%

Chemical structures of catalysts **13** and **14**.

1). From the notion that the transformation of **11** into **12** might be catalyst dependent, we turned to Grubbs' second generation Ru imidazole catalyst **14**.²⁰ Using the conditions

(16) To the best of our knowledge, the only other example of the formation of a tetrasubstituted enol ether using metathesis also came from our laboratory. See: Cox, J. M. Ph.D. Dissertation, The University of Arizona, Tucson, Arizona, 2002.

(17) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

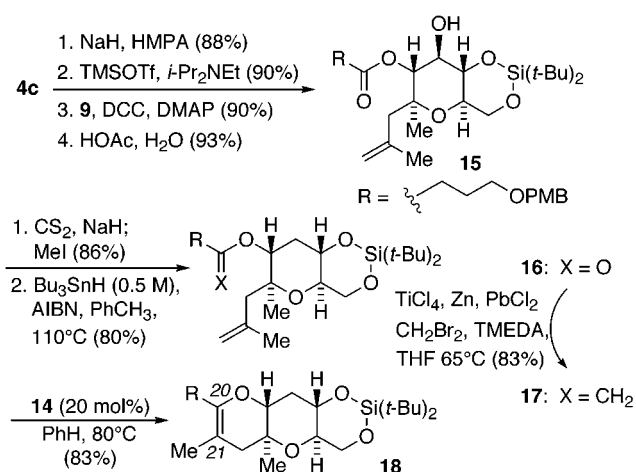
(18) Other enol ether-forming protocols (Tebbe, Petasis) were even less successful in our hands.

(19) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

that had been successful for us previously (rt, benzene, 15% catalyst),^{6c,15f} we only recovered starting material when **11** was subjected to **14** (entry 2). The enhanced stability of **14** at elevated temperatures turned out to be critical;²¹ subjecting **11** to **14** at 65 °C resulted in the generation of a small amount (5%) of the tetrasubstituted enol ether **12** (entry 3). We were pleasantly surprised to find that we could isolate **12** in 82% yield by simply increasing the temperature of the reaction to 80 °C (entry 4).²²

While pleased with the formation of **12**, we were not satisfied with the reactions leading up to **12**. From the notion that the C(25) TBDPS ether might be hindering functionalization at C(24), we opted to postpone the RCM reaction until after C(25) deoxygenation. Toward this goal, selective removal of the TBDPS group gave the corresponding C(24),C(25) diol.^{23,24} Conversion of the diol into the C(25) TMS ether provided **15** after acylation with **9** and removal of the TMS group using HOAc. We were encouraged to find that the esterification of the C(25) TMS analogue of **4c** was much easier than it had been for **4c** itself. Methyl xanthate formation and free radical-induced deoxygenation²⁵ provided enol ether precursor **16**. By subjecting **16** to the Takai

Scheme 1



procedure, we isolated **17** in 83% yield. This experiment clearly validates the notion that our difficulties with the derivatization of **4c** and **10** had been due to the steric

(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(21) See ref 20 and: Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(22) We believe that there could be two reasons for the need for elevated temperatures: (1) the inherent difficulty associated with generating tetrasubstituted enol ethers; (2) the reaction may be proceeding through a relatively unreactive Fischer carbene intermediate prior to cyclization. For an excellent study on the formation and reactivity of Fischer carbenes from enol ethers and **14**, see: Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153.

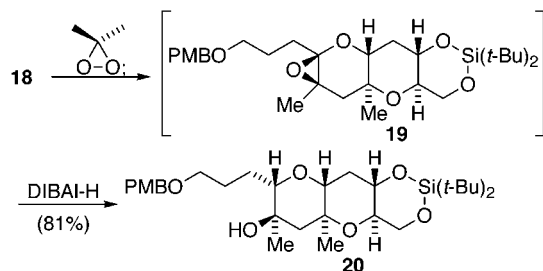
(23) Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.

(24) Attempts to selectively remove the TBDPS group from **10** were unsuccessful.

(25) Paquette, L. A.; Oplinger, J. A. *J. Org. Chem.* **1988**, *53*, 2953.

environment about C(24). RCM utilizing the conditions that had been successful for **11** provided tetrasubstituted enol ether **18**.²⁶

To complete the gambierol F-ring, it remained to oxidize C(21) and reduce C(20). Although hydroboration and oxidation would be the conventional method for carrying out this transformation,²⁷ we targeted a single flask dioxirane oxidation/DIBAL reduction approach.²⁸ Oxidation of **18** with DMDO and reduction of the resulting glycal anhydride (i.e., **19**) using DIBAL provided **20** as a 10:1 mixture of diastereomers in 91% yield.²⁹ With the successful reduction, we had completed the synthesis of the F-ring and the C(21) and C(23) angular methyl groups.



Our final challenge for the F–H coupling precursor was the synthesis of the H-ring. From the possibilities,³⁰ we opted to examine an acid-mediated cyclization sequence. To this end, we removed the cyclic silylene group and then sequentially converted the primary alcohol into the corresponding triflate and the secondary alcohol into the corresponding TBDMS ether to give **21**. The remaining carbon atoms for the H-ring were introduced by coupling triflate **21** with allyl cuprate.³¹ Hydroboration/oxidation and Swern oxidation of the resulting primary alcohol gave aldehyde **23**. Finally, tricyclic oxepene **24** was generated from **23** in an

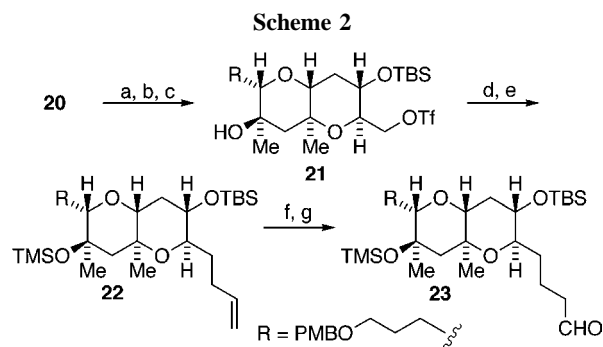
(26) We also attempted to cyclize **17** using Schrock's catalyst **13** without success.

(27) Hydroboration of cyclic enol ethers has been applied to the synthesis of polycyclic ether natural products. For a selected example, see: Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Konstantinos, A.; A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599.

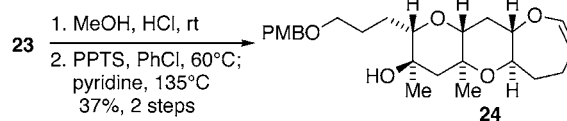
(28) For other examples of this transformation, see ref 8 and: Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616.

(29) Minor product from this coupling is diastereomeric at C(20). We believe that this material comes from the direct reduction of **19**.

(30) Another possibility would involve an RCM sequence. We have previously demonstrated the generation of oxepenes using RCM; see ref 6c.



unoptimized 37% overall yield by first converting **23** into a mixture of the corresponding cyclic and acyclic acetals and then by subjecting the mixture to PPTS, pyridine, and heat according to the protocol that we had developed earlier.³²



In summary, we have synthesized the F–H subunit of the marine ladder toxin gambierol utilizing a C-glycoside-centered strategy. Of note in these studies is our discovery that TBDPS substitution at C(25) influenced the formation of a C(23) C-glycoside. Also noteworthy was the use of the second generation Grubbs' catalyst in the synthesis of tetrasubstituted enol ethers **12** and **18** using enol ether-olefin RCM.

Acknowledgment. We are grateful to the National Institutes of Health, General Medical Sciences (GM56677), for support of this work. We would like to thank Dr. Charles Mayne for help with NMR experiments and Mr. Elliot M. Rachlin for help in obtaining mass spectra.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2–5**, **15–18**, and **20–24**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(31) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726.

(32) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601.