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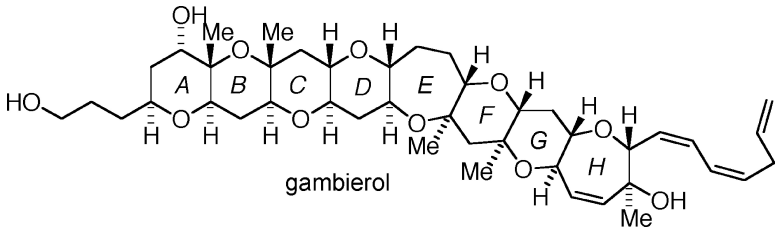

gambierol

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The Total Synthesis of Gambierol

Henry W. B. Johnson, Utpal Majumder, and Jon D. Rainier*

University of Utah, Department of Chemistry, 315 South 1400 East, Salt Lake City, Utah 84112

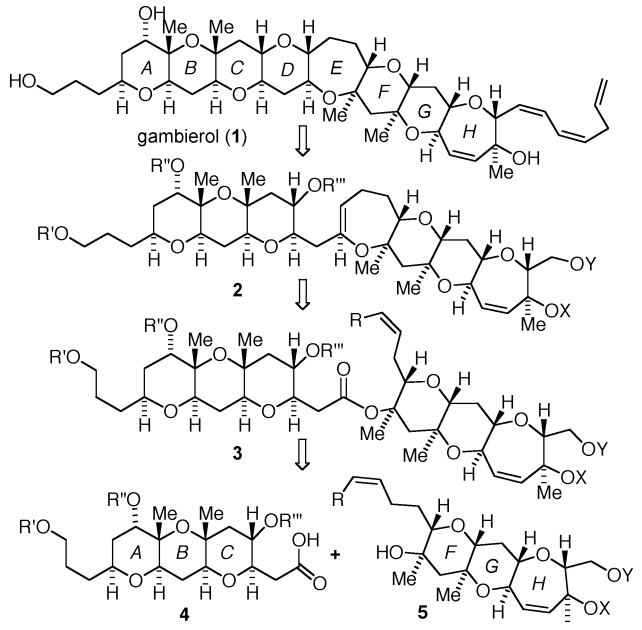
Received November 1, 2004; E-mail: rainier@chem.utah.edu

The unique structural features of the marine polyether toxins, when combined with their interesting biological properties, have attracted the attention of the synthetic chemistry community.[1] Representative of this family is gambierol, a ladder toxin isolated from the cultured cells of *Gambierdiscus toxicus* and published in 1993 by Yasumoto and co-workers.[2] Gambierol has shown toxicity against mice (LD_{50} 50 μg/kg) with symptoms resembling those of the ciguatoxins, inferring the possibility that gambierol is involved in ciguatera poisoning.[3] To date, two total syntheses of gambierol have been accomplished.[4] Herein we describe our work resulting in the total synthesis of this interesting target.

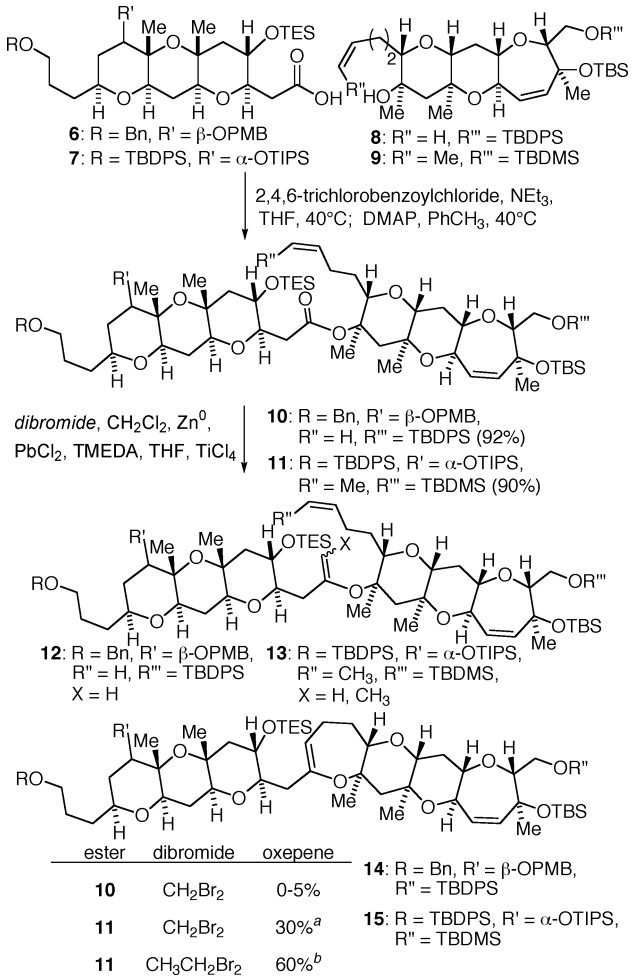
Our plan to synthesize gambierol was a convergent one that centered on the use of an iterative *C*-glycoside/enol ether−olefin ring-closing metathesis strategy to form the subunits followed by an enol ether−olefin ring-closing metathesis reaction to generate gambierol's octacyclic core (Scheme 1). We found it attractive that the subunit coupling chemistry would test the scope and limitations of enol ether−olefin ring-closing metathesis chemistry; these reactions had not been employed on substrates as complex as **3**.[5,6] After the ring closing metathesis, reductive cyclization and incorporation of the side chain would deliver gambierol.

The successful implementation of this plan is illustrated in Schemes 2 and 3. Yamaguchi coupling using equimolar quantities of the A−C and F−H precursors **6** (**7**) and **8** (**9**) provided esters **10** (**11**) in high yield.[7] To our dismay, attempts to convert ester **10** into acyclic enol ether RCM precursor **12** using the Takai−Utimoto titanium methylidene protocol were not successful.[8] Instead, we observed nearly complete decomposition of the terminal olefin and

Scheme 1



Scheme 2



ester	dibromide	oxepene
10	CH_2Br_2	0-5%
11	CH_2Br_2	30%[a]
11	$CH_3CH_2Br_2$	60%[b]

a trace amount of cyclic enol ether **14**.[9−11] In an effort to inhibit alkene decomposition, we next examined the reaction of internal olefin **11**. Surprisingly, this modification also failed to give acyclic enol ether (e.g., **13**, X = H). Instead, it produced an increased amount of cyclic material (e.g., **15**), albeit in a capricious 10−30% yield. Along with cyclic product, significant quantities (10−20%) of the terminal olefin corresponding to **10** were produced along with a number of unidentified products that seemed to result from the decomposition of the terminal olefin. From all of these experiments it was apparent that the presumed titanium methylidene from the Takai−Utimoto reagent was preferentially reacting with the olefin and that this reaction was not regioselective.[12] If our analysis was correct, we believed that the use of a substituted titanium alkylidene reagent in the place of the normally used methylidene reagent would extend the lifetime of the internal olefin and, in theory, lead to a higher yield of cyclic enol ether. That is, were we to use 1,1-dibromoethane instead of 1,1-dibromomethane

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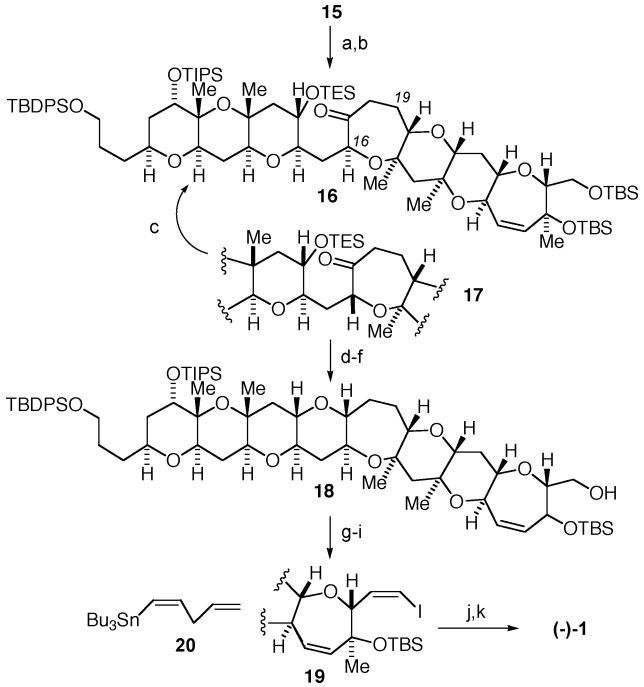
Scheme 3 [a]



[a] Reaction conditions: (a) Dimethyldioxirane, CH_2Cl_2, −78 to 0 °C; DIBAL, CH_2Cl_2, 90% (10:1 mixture). (b) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 97%. (c) imidazole, toluene, 110 °C, 100% (4:1 mix of **14**:**15**). (d) CSA, MeOH, 0 °C, 90%. (e) $Zn(OTf)_2$, EtSH, CH_2Cl_2, rt, 91%. (f) Ph_3SnH, AIBN, toluene, 110 °C, 95%. (g) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 98%. (h) CHI_3, PPh_3. KO*t*-Bu, 0 °C, 95%. (i) Zn−Cu couple, MeOH, AcOH, 0 °C, 85%. (j) SiF_4, CH_3CN, CH_2Cl_2, 0 °C, 89%. (k) **18**, Pd_2dba_3·$CHCl_3$, $P(furyl)_3$, CuI, DMSO, 40 °C, 75%.

in the preparation of the Takai−Utimoto reagent, regioselectivity would not be an issue; reaction with the olefin in the undesired sense would simply regenerate **11** or the olefin isomer of **11**; eventually, the alkylidene would react with the olefin in the desired sense and lead to the formation of cyclic material. We were extremely pleased to find that our analysis of this transformation was accurate: the reaction of **11** with the titanium alkylidene from 1,1-dibromoethane provided cyclic enol ether **15** in 60% yield. Interestingly, for the first time in our work with the gambierol skeleton, we also isolated a 30% yield of acyclic enol ether **13** (X = CH_3).[13]

Having overcome the E-ring problem, we set out to convert **15** into gambierol's octacyclic core (Scheme 3). Single-flask dimethyl dioxirane (DMDO) oxidation of the oxepene and reduction of the resulting anhydride with DIBAL resulted in the formation of the C(17) alcohol in 90% yield as a 10:1 mixture of readily separable diastereomers. Interestingly, the major diastereomer was the result of epoxidation on the same face of **15** as the C(21) methyl group.[14] Oxidation of the alcohols gave diastereomeric ketones **16** and **17**. The minor isomer (i.e., **17**) was equilibrated to the major, desired isomer using imidazole at elevated temperature. Completion of the gambierol octacycle was accomplished by employing a reductive cyclization sequence to the D-ring.[15] That is, selective removal of the TES and primary TBS groups using CSA gave the corresponding hydroxy ketone; *O*,*S*-ketal formation and free-radical reduction completed the generation of the gambierol core structure.

With the octacyclic skeleton in hand we turned to Yamamoto and Sasaki's protocols to incorporate the skipped triene side chain and to complete the synthesis.[4,16] Oxidation of **18** to the aldehyde was followed by formation of the corresponding diiodolefin.[17] Stereoselective reduction,[4c,d] global deprotection,[18] and Stille coupling of the resulting triol with dienyl stannane **20**[4c,d] provided (−)-gambierol. The spectroscopic and physical data for synthetic gambierol were identical to that reported previously.[2,4]

In conclusion, a highly concise total synthesis of gambierol has been achieved utilizing our iterative *C*-glycoside/metathesis methodology. The longest linear sequence to the target was 44 steps from D-glucal with a 1.2% overall yield. Perhaps most impressive is the efficiency of the coupling chemistry where only 12 steps were required to generate gambierol from the A−C and F−H subunits. This compares very favorably with previous work in this area and will significantly simplify our efforts to synthesize and study analogues of this agent. We will report our efforts along these lines in due course.

Acknowledgment. This manuscript is dedicated to our mentor and friend, Professor Amos B. Smith, III on the occasion of his 60th birthday. We are grateful to the National Institutes of Health, General Medical Sciences (GM56677) for support of this work. We thank Dr. Charles Mayne for help with NMR experiments and Dr. Elliot M. Rachlin for help in obtaining mass spectra.

Supporting Information Available: Characterization data and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews on polycyclic ethers see: (a) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293. (b) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228.
(2) (a) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361. (b) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 97.
(3) For biological studies on gambierol see ref 1b and: (a) Fuwa, H.; Kainuma, K.; Tachibana, K.; Tsukano, C.; Satake, M.; Sasaki, M. *Chem. Eur. J.* **2004**, *10*, 4894. (b) Ito, E.; Suzuki-Toyota, F.; Tashimori, K.; Fuwa, H.; Tachibana, K.; Sataki, M.; Sasaki, M. *Toxicon 42*, **2003**, 733. (c) Fuwa, H.; Kainuma, H.; Satake, M.; Sasaki, M. *Biorg. Med. Chem. Lett.* **2003**, *13*, 2519.
(4) (a) Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2981. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983. (c) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46. (d) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893.
(5) For a recent review see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(6) (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.
(7) (a) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919. (b) Majumder, U. Cox, J. M.; Rainier, J. D. *Org Lett.* **2003**, *5*, 913.
(8) (a) Okazoe, T.; Takai, K. *J. Org. Chem.* **1987**, *52*, 4410. (b) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.
(9) Attempts to generate the acyclic enol ether using other alkylidene reagents (Tebbe, Petasis, Takeda) were also unsuccessful.
(10) The Tebbe reagent has been used to carry out related cyclizations. (a) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855. (b) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843. (c) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (d) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335.
(11) For a related transformation that utilizes the Takeda protocol see: Uehara, H.; Oishi, T.; Inoue, M.; Shoji, M.; Nagumo, Y.; Kosaka, M.; Le Brazidec, J.-Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 6493.
(12) Mechanistically, we believe that cyclic product results from an olefin metathesis, carbonyl olefination sequence. Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997.
(13) We have been able to convert **13** (X = CH_3) into **15** in an unoptimized 60% yield using the Grubbs 2 catalyst.
(14) At present, we do not have a clear explanation for the facial selectivity in the DMDO oxidation of **15**. Sasaki observed similar selectivity in the hydroboration of a related oxepene in his gambierol work.[4a,b]
(15) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.
(16) Kadota, I.; Ohno, A.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6373.
(17) Michel, P.; Rassat, A. *Tetrahedron Lett.* **1999**, *40*, 8579.
(18) Corey, E. J.; Yi, K. Y. *Tetrahedron Lett.* **1992**, *33*, 2289.

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