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Total Synthesis of Gambierol

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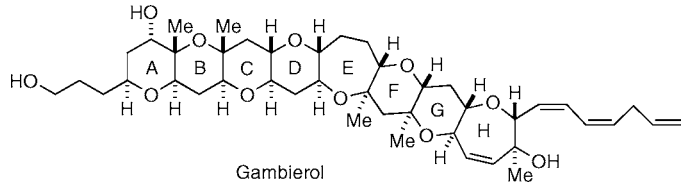
ABSTRACT



Gambierol

The total synthesis of gambierol has been achieved utilizing an oxiranyl anion strategy in an iterative manner. Synthetic highlights of this route include direct carbon−carbon formation on epoxides, sulfonyl-assisted 6-*endo* cyclization, and expansion reaction of tetrahydropyranyl rings to oxepanes to forge the polycyclic architecture of the target molecule.

Gambierol (**1**) was isolated as a neurotoxin from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus* in 1993[1] and classified as a member of the polycyclic ether family of marine toxins.[2] The toxin exhibits potent toxicity against mice at LD_{50} 50 μg/kg (ip), and its symptoms occurring in mice resemble those shown for ciguatoxins, indicating that gambierol is also responsible for ciguatera seafood poisoning. The ability of gambierol to inhibit the binding of dihydrobrevetoxin B to voltage-gated sodium channels[3] has also attracted attention, leading to structure−activity relationship (SAR) studies[4] and evaluation of its molecular target on the voltage-gated potassium channels.[5]

The structure consists of a ladder-shaped *trans*-fused octacyclic ring system that includes 18 stereogenic centers and a partially conjugated triene side chain, including a conjugated (*Z*,*Z*)-diene system. The complex architecture and the need for biological active analogues for SAR study continue to interest organic chemists, and three total syntheses have been reported,[6] as well as related methodology studies.[7] We were motivated to construct gambierol by a different strategy through the implementation of our own methods. We describe herein a new approach to the total synthesis of gambierol (**1**).

Our approach includes the reaction of sulfonyl-stabilized oxiranyl anions,[8] which enables direct and efficient carbon−carbon bond formation on an oxirane ring,[9] sulfonyl-assisted 6-*endo* cyclization,[10] and a ring-expansion reaction with trimethylsilyldiazomethane.[11] We envisioned that two seven-membered rings in **2**

(1) (a) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361–362. (b) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *54*, 12630–12673.

(2) For reviews on marine polycyclic ethers, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909. (b) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293–314. (c) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228–242.

(3) Inoue, M.; Hirama, M.; Satake, M.; Sugiyama, K.; Yasumoto, T. *Toxicon* **2003**, *41*, 469–474.

(4) Fuwa, H.; Kainuma, N.; Tachibana, K.; Tsukano, C.; Satake, M.; Sasaki, M. *Chem.−Eur. J.* **2004**, *10*, 4894–4909.

(5) (a) Ghiaroni, V.; Sasaki, M.; Fuwa, H.; Rossini, G. P.; Scalera, G.; Yasumoto, T.; Pietra, P.; Bigiani, A. *Toxicol. Sci.* **2005**, *85*, 657–665. (b) Louzao, M.; Cagide, E.; Vieytes, M. R.; Sasaki, M.; Fuwa, H.; Yasumoto, T.; Botana, L. M. *Cell. Physiol. Biochem.* **2006**, *17*, 257–268. (c) Cuypers, E.; Yanagihara, A.; Rainier, J. D.; Tytgat, J. *Biochem. Biophys. Res. Commun.* **2007**, *361*, 214–217. (d) LePage, K. T.; Rainier, J. D.; Johnson, H. W. B.; Baden, D. G.; Murray, T. F. *J. Pharmacol. Exp. Ther.* **2007**, *323*, 174–179. (e) Cuypers, E.; Abdel-Mottaleb, Y.; Kopljar, I.; Rainier, J. D.; Raes, A. L.; Snyders, D. J.; Tytgat, J. *Toxicon* **2008**, *51*, 974–983. (f) Pietra, F. *J. Phys. Org. Chem.* **2008**, *21*, 997–1001. (g) Kopljar, I.; Labro, A. J.; Cuypers, E.; Johnson, H. W. B.; Rainier, J. D.; Tytgat, J.; Snyders, D. J. *Proc. Natl. Acad. Sci. U.S.A* **2009**, *106*, 9896–9901.

(6) (a) Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2981–2984. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983–14992. (c) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46–47. (d) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893–11899. (e) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848–849. (f) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. *Chem.−Eur. J.* **2006**, *12*, 1736–1746. (g) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *Chem.−Eur. J.* **2006**, *12*, 1747–1753.

(7) (a) Saito, T.; Takeuchi, T.; Matsuhashi, M.; Nakata, T. *Heterocycles* **2007**, *72*, 151–156. (b) Saito, T.; Nakata, T. *Org. Lett.* **2009**, *11*, 113–116.

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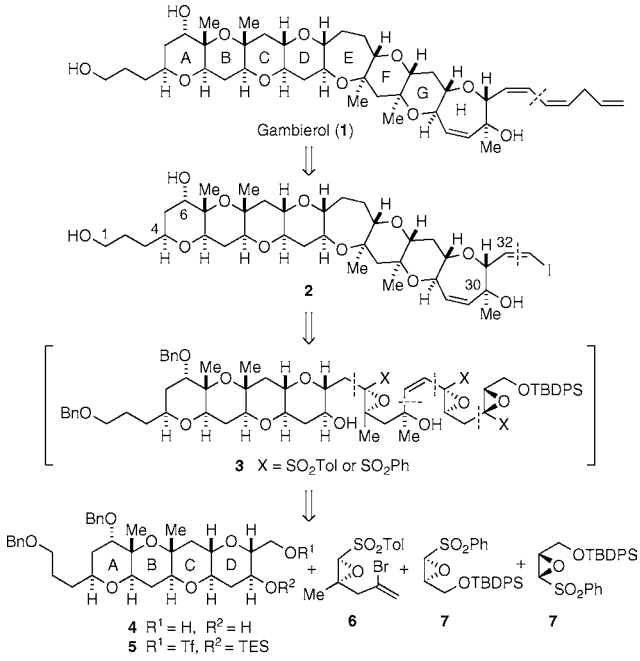
would be constructed by an expansion reaction of tetrahydropyranyl rings at suitable stages of synthesis (Scheme 1), so we tentatively

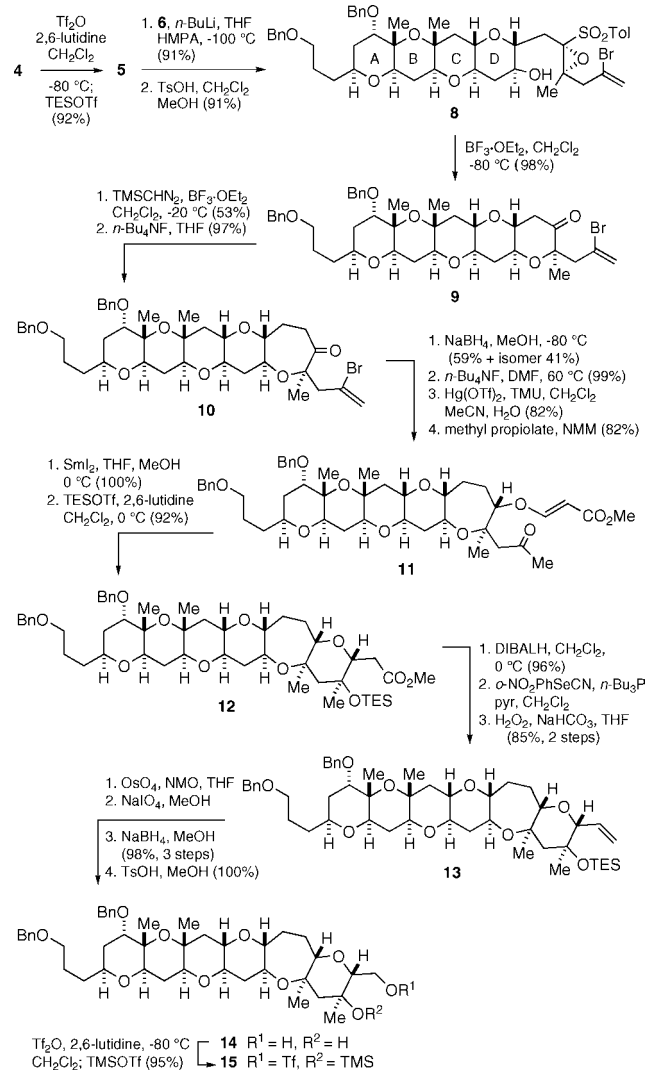
Scheme 1. Retrosynthetic Analysis of Gambierol (**1**)



regarded **3** as an imaginary precursor and dissected it at the indicated bonds, furnishing the ABCD ring diol **4** and epoxy sulfones **6** and **7** as potential building blocks.

Synthesis of the E ring started from the coupling reaction of the oxiranyllithium generated from epoxy sulfone **6**[12] with the ABCD ring triflate **5** prepared from diol **4**[13] in a one-pot procedure (Scheme 2). Treatment of a mixture of **5** and **6** with *n*-BuLi in THF−HMPA at −100 °C afforded **8** in 83% yield after desilylation. A sulfonyl-assisted 6-*endo* cyclization[10b] was effected by BF_3·OEt_2 to quantitatively provide ketone **9**. The ketone was then subjected to a ring-expansion reaction with trimethylsilyldiazomethane in the presence of BF_3·OEt_2 to furnish the desired oxepane **10** in 51% overall yield after desilylation of the resulting α-trimethylsilyl ketone with TBAF. Reduction of ketone **10** with $NaBH_4$ and dehydrobromination with TBAF in DMF[14] gave a terminal acetylene. Hydration of the acetylene with a catalytic amount of $Hg(OTf)_2$[15] followed by a hetero-Michael reaction with methyl

Scheme 2. Preparation of Hexacyclic Triflate **15**



propiolate provided keto acrylate **11**. Treatment of **11** with SmI_2 in the presence of methanol effected ketyl radical cyclization[16] to afford, after silylation, hexacyclic ester **12** in 92% yield as a single diastereoisomer with sterically congested 1,3-diaxial dimethyl groups. The ester was then reduced with DIBALH to furnish an alcohol, which was converted to olefin **13** via *o*-nitrophenyl selenide[17] in 82% overall yield. Subsequent oxidative cleavage of the double bond followed by reduction of the resulting aldehyde provided the ABCDEF ring diol **14**, which was transformed into triflate **15** in 93% overall yield for the five steps.

Installation of the G and H rings was based on the use of an oxiranyl anion strategy carried out in an iterative manner, which involved the reactions of epoxy sulfone **7**[11] and triflates **15** and **19** (Scheme 3). Thus, lithiation of **7** with *n*-BuLi at −100 °C in the presence of triflate **15** furnished epoxy sulfone **16** in 93% yield. Exposure of **16** to BF_3·OEt_2 caused 6-*endo* cyclization, which formed the G ring ketone **17** in 91% yield. Stereoselective reduction of the ketone and removal of the TBDPS group afforded diol **18**, which was then subjected to one-pot triflation and silylation to furnish

(8) For reviews on oxiranyl anions, see: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. (b) Mori, Y. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1997; Vol. 17, pp 183−211. (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642.

(9) (a) Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc. Perkin Trans. 1* **1991**, 897–908. (b) Mori, Y.; Yaegashi, K.; Iwase, K.; Yamamori, Y.; Furukawa, H. *Tetrahedron Lett.* **1996**, *37*, 2605–2608.

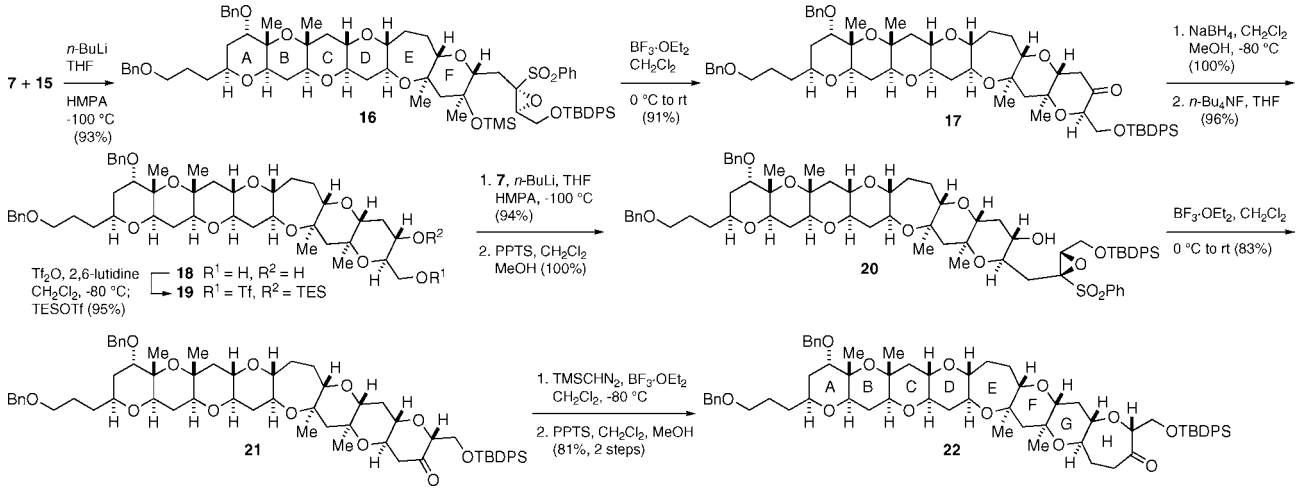
(10) (a) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158–8159. (b) Furuta, H.; Takase, T.; Hayashi, H.; Noyori, R.; Mori, Y. *Tetrahedron* **2003**, *59*, 9767–9777.

(11) Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917–12932.

(12) Prepared from 4-bromopent-4-en-2-one and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide according to the following: Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130–3136.

(13) Furuta, H.; Hase, M.; Noyori, R.; Mori, Y. *Org. Lett.* **2005**, *7*, 4061–4064.

Scheme 3. Synthesis of Octacyclic Ketone **22**

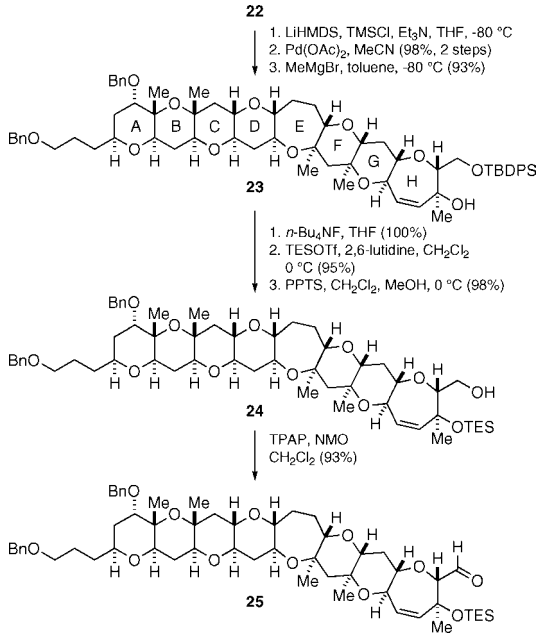


triflate **19** in 91% for the three steps. The second coupling reaction of **19** with the oxiranyllithium of **7** provided, after desilylation, epoxy sulfone **20** in 94% yield. The BF_3-promoted cyclization of **20** resulted in the formation of octacyclic ketone **21** in 83% yield. Conversion of the ketone to the 7-membered H ring ketone **22** occurred smoothly with trimethylsilyldiazomethane in the presence of $BF_3{\cdot}OEt_2$. This ring enlargement was achieved in an excellent 81% yield (two steps) compared with the case of the E ring formation.

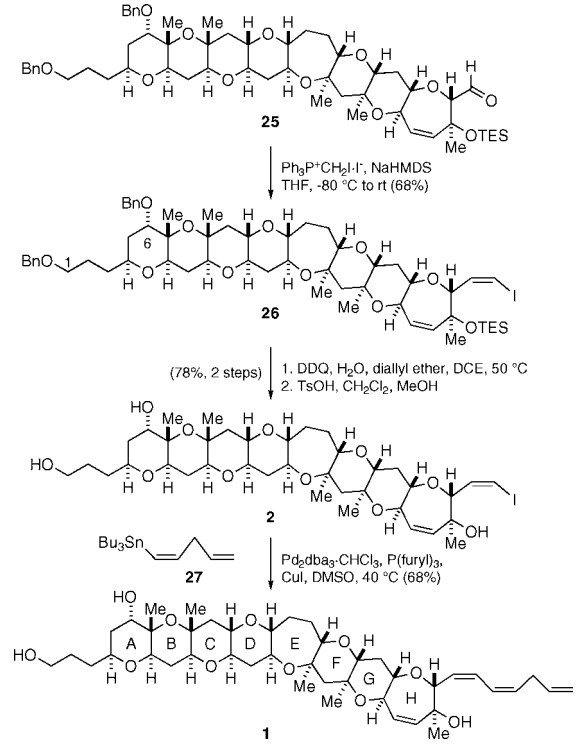
Octacyclic ketone **22** was then elaborated to the desired unsaturated aldehyde **25** by the sequence depicted in Scheme 4. Thus, treatment of ketone **22** with LiHMDS in the presence of TMSCl and Et_3N followed by dehydrosilylation of the corresponding enol silyl ether with $Pd(OAc)_2$[18] provided an enone, which was subjected to methylation with MeMgBr in toluene[6b,d] to afford tertiary alcohol **23** in 91% overall yield as a single diastereoisomer. The alcohol **23** was converted into the primary alcohol **24** by a three-step procedure in 93% overall yield. Oxidation of the alcohol with TPAP provided aldehyde **25** in 93% yield.

Finally, our attention turned to incorporation of the skipped triene side chain to complete the total synthesis (Scheme 5). In this context, the Stille coupling reaction utilizing vinyl iodide **2** and vinyl stannane **27** is a powerful and reliable

Scheme 4. Synthesis of Aldehyde **25**



Scheme 5. Synthesis of Gambierol



method, as demonstrated in the previous studies.[6] In these studies, the robust C(1) and C(6) benzyl groups of the TBS ether analogues of **22** or **23** were replaced by silyl groups prior to installation of a (*Z*)-vinyl iodide moiety. However, if debenzylation in the presence of the vinyl iodide functionality were feasible, a shorter route to reaching **2** would be made possible. To this end, aldehyde **25** was subjected to iodomethylenation with $Ph_3P^+CH_2I{\cdot}I^-$ and NaHMDS[19] to afford (*Z*)-vinyl iodide **26** in 68% yield.[20] Debenzylation of **26** was now critical for successful evolution of our route, as it needed to be executed in the presence of labile (Z)-vinyl iodide, cyclic allylic ether, and TES ether functionalities. Upon considerable experimentation, it was found that gentle heating of **26** with DDQ in the presence of water and diallyl ether in 1,2-dichloroethane at 50 °C induced debenzylation,[21] leading to a 78% yield of the desired triol **2** after removal of TES ether. Finally, Stille coupling of triol **2** with dienyl stannane **27**[22] was carried out by using Kadota and Rainier's protocols[6c,e] to provide gambierol (**1**) in 68% yield. The spectroscopic and physical data for synthetic gambierol were identical to those reported previously.[1,6]

In conclusion, total synthesis of gambierol has been achieved utilizing an oxiranyl anion strategy in an iterative manner. The salient features of the route include: (1) direct carbon−carbon bond formation on an oxirane ring and the subsequent sulfonyl-assisted 6-*endo* cyclization; (2) a ring-expansion approach to seven-membered ether rings; (3) a successful implementation of debenzylation in the presence of labile functional groups. Further application of this oxiranyl anion coupling strategy to other marine polycyclic ethers is in progress.

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

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(14) (a) Okutani, M.; Mori, Y. *Tetrahedron Lett.* **2007**, *48*, 6856–6859. (b) Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442–444.

(15) Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. *Chem. Lett.* **2002**, 12–13.

(16) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron. Lett.* **1999**, *40*, 8859–8862.

(17) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(18) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(19) (a) Seyferth, D.; Heeren, J. K.; Singh, G.; Grim, S. O.; Hughes, W. B. *J. Organomet. Chem.* **1966**, *5*, 267–274. (b) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174. (c) Goundry, W. R. F.; Baldwin, J. E.; Lee, V. *Tetrahedron* **2003**, *59*, 1719–1729.

(20) Although the (*E*)-isomer was not obtained in this reaction, the C(31)−C(32) unsaturated iodide was isolated in 27% yield.

(21) Hamajima, A.; Isobe, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2941–2945.

(22) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221.