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Studies toward the Total Synthesis of Gambieric Acids, Potent Antifungal Polycyclic Ethers: Convergent Synthesis of the CDEFG-Ring System

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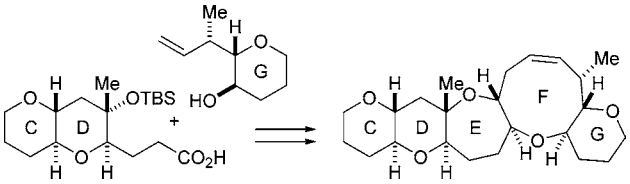
ABSTRACT



A convergent synthetic route to the CDEFG-ring system of gambieric acids, potent antifungal polycyclic ether marine natural products, has been developed. The present synthesis features convergent union of the CD- and G-rings through esterification, formation of the E-ring as a lactone form, stereoselective allylation to set the C_{26} stereocenter, and ring-closing metathesis reaction to construct the nine-membered F-ring.

A number of polycyclic ether natural products with potent and diverse biological activities have been isolated from marine sources.[1] Gambieric acids A−D (**1**−**4**, Figure 1) were isolated by the Yasumoto group from the culture media of the marine dinoflagellate, *Gambierdiscus toxicus*, which is the causative organism responsible for ciguatera seafood poisoning.[2] These polycyclic ethers have attracted considerable interest because of their potent antifungal activity against a variety of filamentous fungi.[2c] Their antifungal activity against *Aspergillus niger* by the paper disk method was 2000 times greater than that of amphotericin B, and they exhibited only moderate toxicity toward mammalian cells. These findings make them potential lead compounds for the discovery of antifungal agents.[2] In this letter, we describe a convergent synthesis of the CDEFG-ring system **5** of gambieric acids.[3]

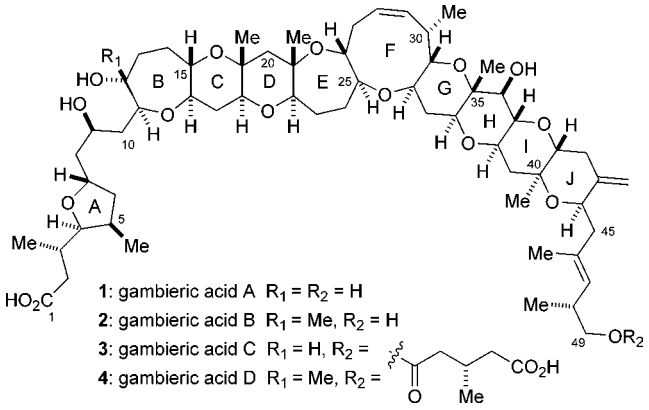


Figure 1. Structures of gambieric acids A−D.

During our studies toward the total synthesis of ciguatoxins, we have previously reported a convergent route to the

(1) 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**, 293−314. (c) Yasumoto, T. *Chem. Rec.* **2001**, *3*, 228−242.

(2) (a) Nagai, H.; Torigoe, K.; Satake, M.; Murata, M.; Yasumoto, T.; Hirota, H. *J. Am. Chem. Soc.* **1992**, *114*, 1102−1103. (b) Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448−5453. (c) Nagai, H.; Mikami, Y.; Yazawa, K.; Gonoi, T.; Yasumoto, T. *J. Antibiot.* **1993**, *46*, 520−522. (d) Morohashi, A.; Satake, M.; Nagai, H.; Oshima, Y.; Yasumoto, T. *Tetrahedron* **2000**, *56*, 8995−9001.

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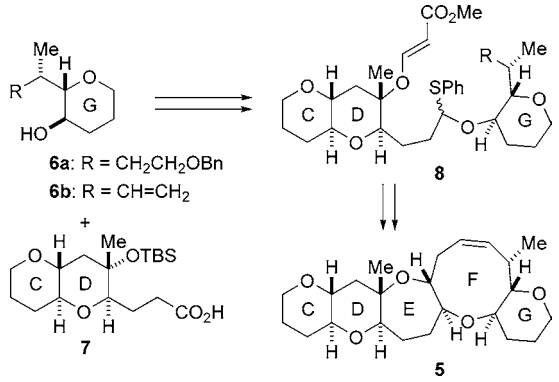
FGH-ring system.[4] The synthesis features an intramolecular radical cyclization to form the seven-membered G-ring with complete stereocontrol and a ring-closing metathesis (RCM) to construct the nine-membered F-ring. Subsequently, this approach was further modified and refined by the Hirama group, culminating in the first total synthesis of ciguatoxin CTX3C.[5] Initially, we planned to synthesize the CDEFG-ring system **5** of gambieric acids by applying this strategy (Scheme 1). The nine-membered F-ring of **5** could be

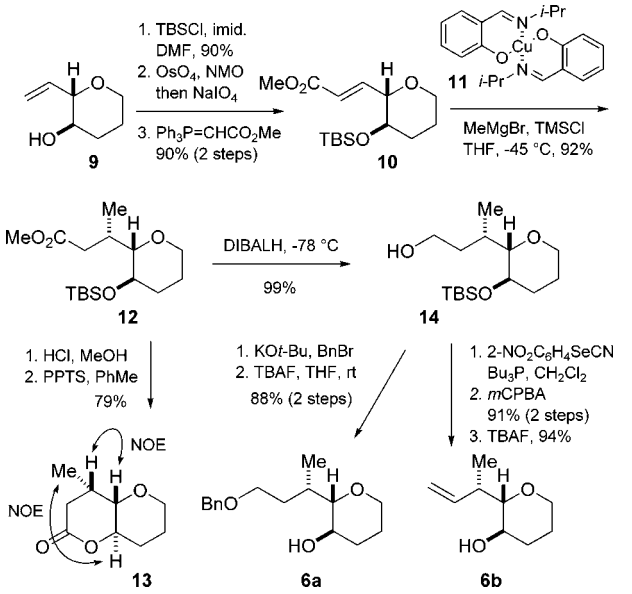
Scheme 1. First Synthesis Plan for the CDEFG-Ring System **5**



constructed by RCM from a precursor diene. In turn, the seven-membered E-ring was envisioned to be formed by an intramolecular radical cyclization of **8**, which would be derived from alcohol **6** and carboxylic acid **7**.

The synthesis of alcohols **6a** and **6b** started with compound **9**[6] (Scheme 2). Protection as the TBS ether and oxidative cleavage of the double bond, followed by Wittig reaction with methyl (triphenylphosphoranilidene)acetate, afforded enoate **10** in 81% yield for the three steps. Treatment of **10** with methylmagnesium bromide in the presence of TMSCl and *i*-propylsalicylaldimine copper(II) complex **11**[7] (THF, −45 °C) gave the desired adduct **12** as the sole product in high yield.[8] The stereochemistry of the newly generated stereocenter was confirmed by conversion to lactone **13** and its NMR analysis as shown. DIBALH reduction of **12**

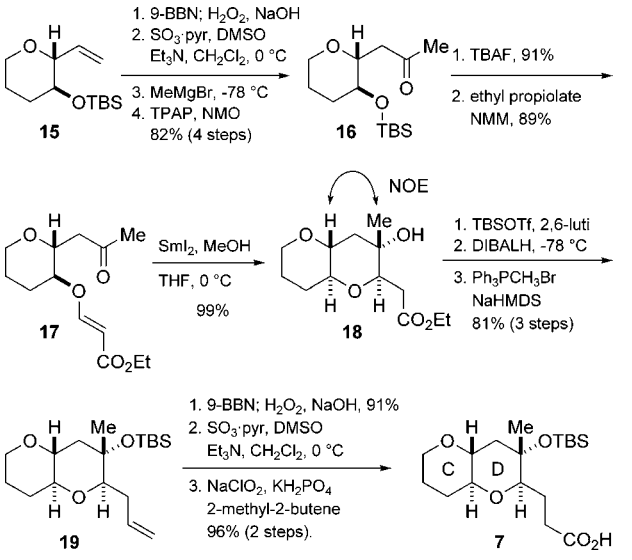
Scheme 2. Synthesis of Alcohols **6a** and **6b**



produced primary alcohol **14** (99%), which upon benzylation followed by desilylation yielded alcohol **6a** in 88% yield for the two steps. Alcohol **14** was converted to a terminal olefin via *o*-nitrophenyl selenide by the method of Grieco and Nishizawa.[9] Subsequent desilylation afforded alcohol **6b** in 85% yield for the three steps.

The synthesis of carboxylic acid **7** commenced with alcohol **15**,[10] which was converted to methyl ketone **16** by a four-step sequence in 82% overall yield (Scheme 3).

Scheme 3. Synthesis of Carboxylic Acid **7**



Following desilylation, treatment of the derived alcohol with ethyl propiolate in the presence of *N*-methylmorpholine (NMM) produced β-alkoxyacrylate **17** in 81% yield over the two steps. Treatment of **17** with samarium(II) iodide in the

(3) For synthetic studies of gambieric acids, see: (a) Kadota, I.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3645−3647. (b) Kadota, I.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3649−3651. (c) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773−1776.

(4) (a) Sasaki, M.; Noguchi, T.; Tachibana, *J. Org. Chem*. **2002**, *67*, 3301−3310. (b) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett*. **1999**, *40*, 1337−1340. (c) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett*. **1998**, *39*, 2783−2786.

(5) (a) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904−1907. (b) Inoue, M.; Uehara, H.; Maruyama, M.; Hirama, M. *Org. Lett.* **2002**, *4*, 4551−4554. (c) Inoue, M.; Hirama, M. *Synlett* **2004**, *4*, 577−595. (d) Inoue, M.; Miyazaki, K.; Uehara, H.; Maruyama, M.; Hirama, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12013−12018. (e) Inoue, M.; Hirama, M. *Acc. Chem. Res*. **2004**, *37*, 961−968.

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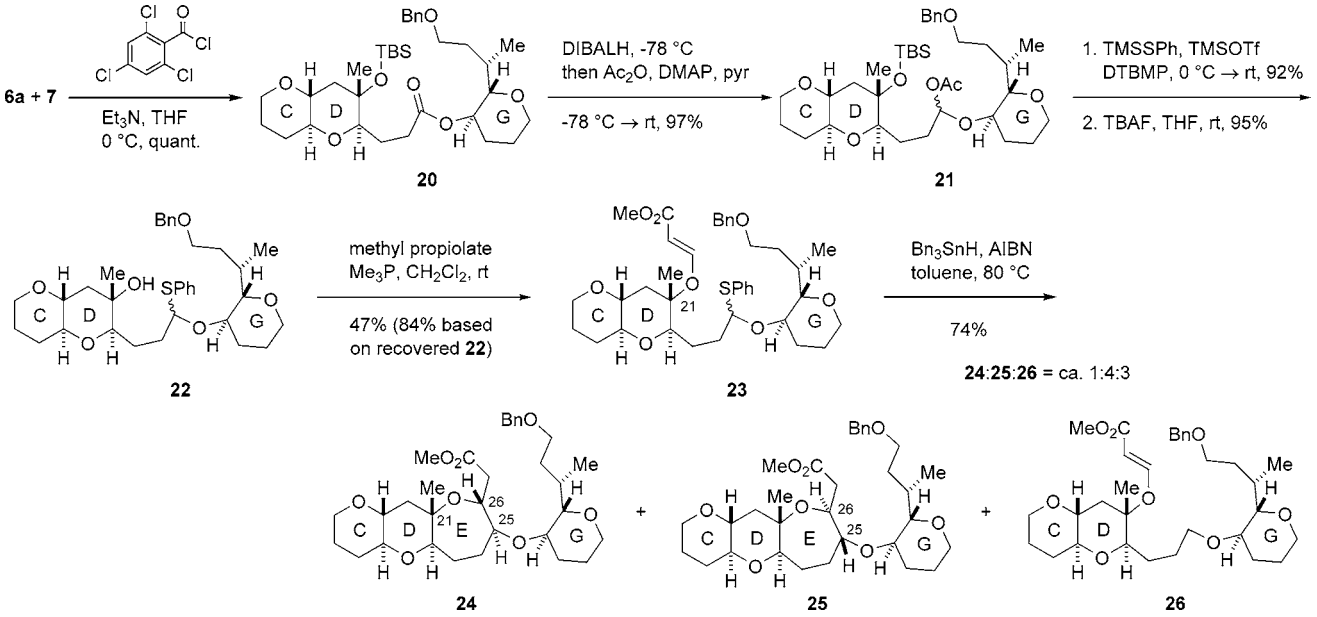
(7) Sakata, H.; Aoki, Y.; Kuwajima, I. *Tetrahedron Lett*. **1990**, *31*, 1161−1164.

(8) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc*. **2004**, *126*, 14374−14376.

Scheme 4. Attempted Synthesis of O-Linked Oxacycle **26**



presence of methanol effected reductive cyclization[11] to deliver bicyclic ester **18** as the sole product in high yield. After protection as the *tert*-butyldimethylsilyl (TBS) ether, DIBALH reduction of the ester moiety to the aldehyde followed by Wittig reaction gave olefin **19** in 81% yield for the three steps. Hydroboration using 9-BBN followed by oxidative workup gave an alcohol (91%), which was then oxidized by a two-step procedure (SO_3·pyr/DMSO then $NaClO_2$) to provide acid **7** in 96% yield for the two steps.

With the desired fragments **6** and **7** in hand, we next turned our attention to their coupling. Yamaguchi esterification of **6a** with **7** proceeded smoothly to afford ester **20** in high yield (Scheme 4). Conversion to the α-acetoxy ether **21** was carried out according to the procedure of Rychnovsky (DIBALH, CH_2Cl_2, −78 °C; then Ac_2O, DMAP, pyridine, −78 °C → room temperature).[12] Subsequent treatment with TMSSPh in the presence of TMSOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) generated, after desilylation, mixed thioacetal **22** in 85% overall yield from **20**. The *β*-alkoxyacrylate unit was attached to the tertiary alcohol by treatment with methyl propiolate and trimethylphosphine to provide **23** in modest yield (47%; 84% yield based on recovered **21**). However, radical cyclization of **23** (Bu_3SnH, AIBN toluene, 80 °C) was sluggish and yielded a complex mixture of the desired O-linked oxepane **24**,[13] its diastereomer **25**, and reduction product **26** in a ratio of ca. 1:4:3, along with recovered **23**. The outcome of this radical cyclization can be explained as follows (Figure 2). Severe steric repulsion between the C_{21}[14] tertiary methyl group and the *β*-hydrogen on the acrylate unit in the transition state structure **A** resulted in a preference for the structure **B**, which leads to **25**. A similar result has been reported by Nakata and co-workers in the SmI_2-mediated reductive cyclization.[15]

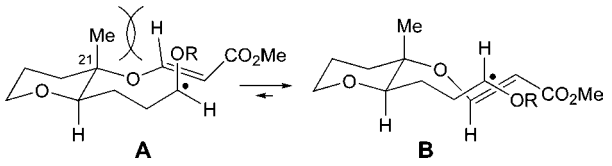


Figure 2. Possible rationale for radical cyclization.

Accordingly, we next investigated an alternative route as summarized in Scheme 5. Alcohol **6b** and carboxylic acid **7**

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

(10) Nicolaou, K. C.; Hwang, C. K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc*. **1990**, *112*, 3040−3054.

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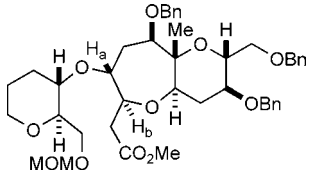
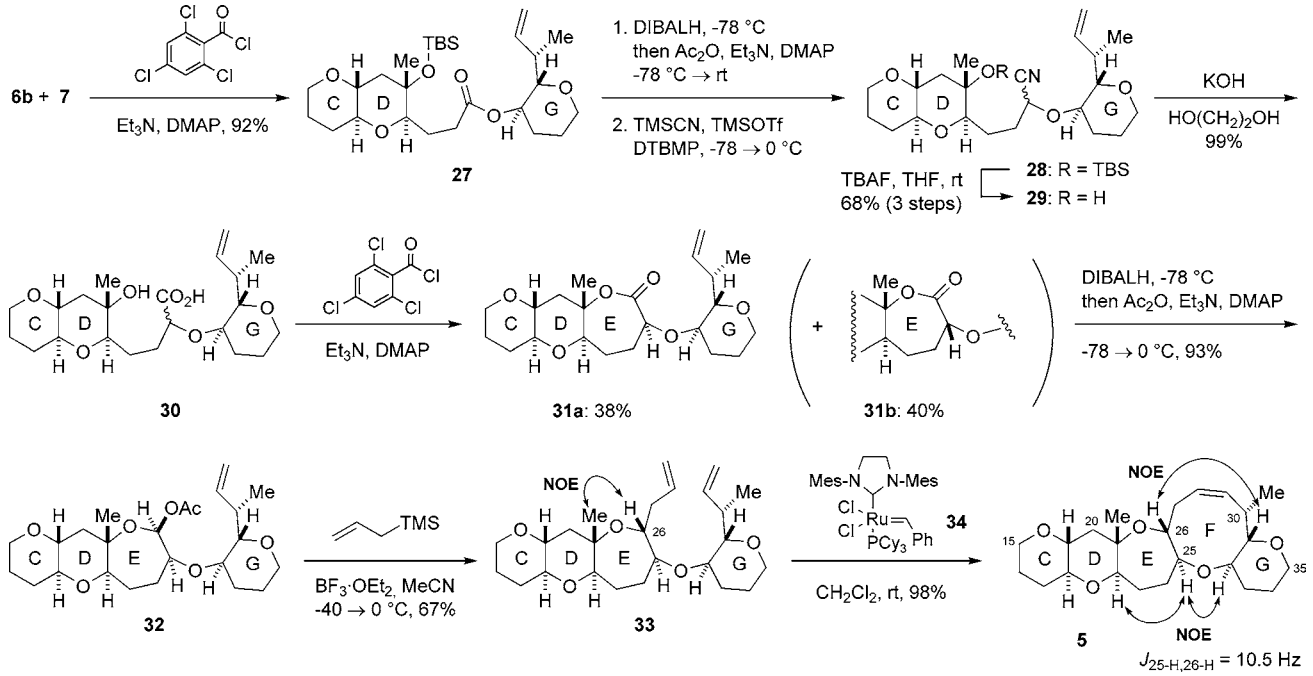
(13) Stereostructure of compound **24** was assigned by NOE between 21-Me and 26-H and the coupling constant, $J_{25,26}$ = 3.5 Hz. In a related O-linked oxepane ring system, a small coupling constant, J = 0 Hz, between H_a and H_b was observed. See: Sasaki, M.; Noguchi, T.; Tachibana, K. *J. Org. Chem*. **2002**, *67*, 3301−3310.



(14) Numbering of carbon atoms of all compounds in this paper corresponds to that of gambieric acid A.

(15) Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahedron Lett*. **2002**, *43*, 8653−8655.

Scheme 5. Synthesis of the CDEFG-Ring System **5**



were coupled through esterification to afford **27** (92%), which was subjected to reductive acetylation to give an α-acetoxy ether as a 3:1 mixture of diastereomers. Subsequent treatment with TMSCN in the presence of TMSOTf and DTBMP generated nitrile **28**,[16] which was desilylated to produce alcohol **29** in 68% yield over the three steps. The nitrile group was hydrolyzed under alkaline conditions to give carboxylic acid **30** as a 1:1 mixture of isomers. Yamaguchi lactonization produced a mixture of seven-membered lactones, which was separated by flash column chromatography to give **31a** and **31b** in 38 and 40% yield, respectively.[17] Reduction of lactone **31a** with DIBALH followed by in situ acetylation produced acetate **32** in 93% yield as the sole product. Upon treatment of **32** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ (MeCN, −40 → 0 °C), stereoselective allylation occurred from the less hindered α-face of the molecule to generate diene **33** in 67% yield. Stereochemistry at the C_{26} position was determined by NOE between 21-Me and 26-H. Finally, construction of the nine-membered F-ring was achieved by the action of the second-generation Grubbs' catalyst **34**[18,19] to furnish the targeted CDEFG-ring system **5** in 98% yield. The stereochemistry of **5** was unambiguously established by NOE experiments and the coupling constant.

In summary, we have developed a synthetic route to the CDEFG-ring system **5** of gambieric acids through convergent union of the CD- and G-rings. Further studies toward the total synthesis of gambieric acids along these lines are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds **10**, **12**−**14**, **6b**, **16**−**19**, **7**, **27**−**33**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Synthesis of α-cyano ether in a related system; see: Oishi, T.; Watanabe, K.; Murata, M. *Tetrahedron Lett.* **2003**, *44*, 7315−7319.

(17) Attempted isomerization of the undesired **31b** to **31a** under various basic conditions was unsuccessful.

(18) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(19) For a recent review, see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.