J|A|C|S
COMMUNICATIONS

Published on Web 12/11/2002

Total Synthesis of Gambierol

Isao Kadota,† Hiroyoshi Takamura,‡ Kumi Sato,‡ Akio Ohno,‡ Kumiko Matsuda,‡ and Yoshinori Yamamoto*,‡

Research Center for Sustainable Materials Engineering, Institute of Multidisciplinary Research for Advanced Materials, and Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Received September 27, 2002; E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp

In recent years, there has been an explosion of interest in biologically active natural products of marine origin.[1] Because of their structural novelty and toxicity, polycyclic ethers are particularly attractive targets for synthetic chemists.[2] Gambierol (**1**), a potent neurotoxin isolated from the cultured cells of *Gambierdiscus toxicus*, has 8 ether rings and 18 stereogenic centers.[3] The compound shows toxicity against mice (LD_{50} 50 μg/kg), and the symptoms resemble those caused by ciguatoxins, inferring the possibility that it is also implicated in ciguatera poisoning.[1] The unique structural features have attracted the attention of synthetic chemists, and a number of strategies have been investigated.[4,5] In this paper, we describe a new approach to the total synthesis of gambierol (**1**).

Figure 1 illustrates our retrosynthetic analysis of **1**. Recently, we developed a convergent method for the synthesis of polycyclic ether frameworks via the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis.[4i,l] On the basis of this methodology, the octacyclic ether framework of **1** was retrosynthetically broken down into the ABC ring segment **3** and the FGH fragment **4** via the diene **2**.

The initial task of the total synthesis was the construction of the octacyclic framework. The carboxylic acid **3** and the alcohol **4**[6] were connected by Yamaguchi conditions[7] to give the ester **5** in 94% yield (Scheme 1). A series of reactions including desilylation with TBAF, acid-catalyzed acetal formation with **6**, and acetal cleavage with TMSI/HMDS furnished the allylic stannane **7** in 77% overall yield.[8] The ester **7** was then subjected to the modified Rychnovsky acetylation. Thus, partial reduction of **7** with DIBALH, followed by treatment of the resulting aluminum hemiacetal with $(CH_2ClCO)_2O$/pyridine/DMAP,[9] gave the α-chloroacetoxy ether **8** as a 3:2 inseparable mixture of diastereoisomers in 88% yield. Treatment of **8** with $BF_3{\cdot}OEt_2$ gave a 2:1 mixture of the desired product **2** and its epimer **9** in 87% yield.[10,11] The diene **2** obtained was subjected to ring-closing metathesis using the second generation Grubbs catalyst **10**[12] to give the octacyclic ether **11** in 88% yield.

We then focused on the modification of the H ring moiety. Hydrolysis of the benzylidene acetal of **11** led to the corresponding diol. Selective protection of the primary alcohol followed by TPAP oxidation of the secondary alcohol gave the ketone **12** in 77% overall yield. Hydrogenation of **12** followed by debenzylation gave the saturated diol. The primary and secondary alcohols were protected by Pv and TIPS groups, respectively, to afford **13** in 80% overall yield. Treatment of **13** with LiHMDS/TMSCl/Et_3N[5] gave the corresponding enol silyl ether, which was subjected to dehydrosilylation with $Pd(OAc)_2$[13] to afford the enone **14** in 92% overall yield. Stereoselective introduction of the methyl group was carried out using MeMgI in toluene[14] to give the tertiary alcohol as a single stereoisomer. TBS protection and subsequent selective deprotection of the primary silyloxy group afforded **15** in 82% overall yield.

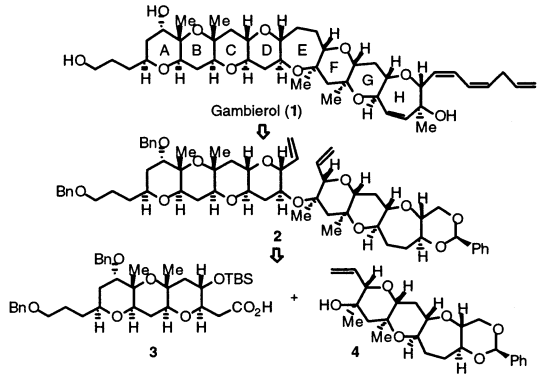


Figure 1. Retrosynthetic analysis of gambierol (**1**).

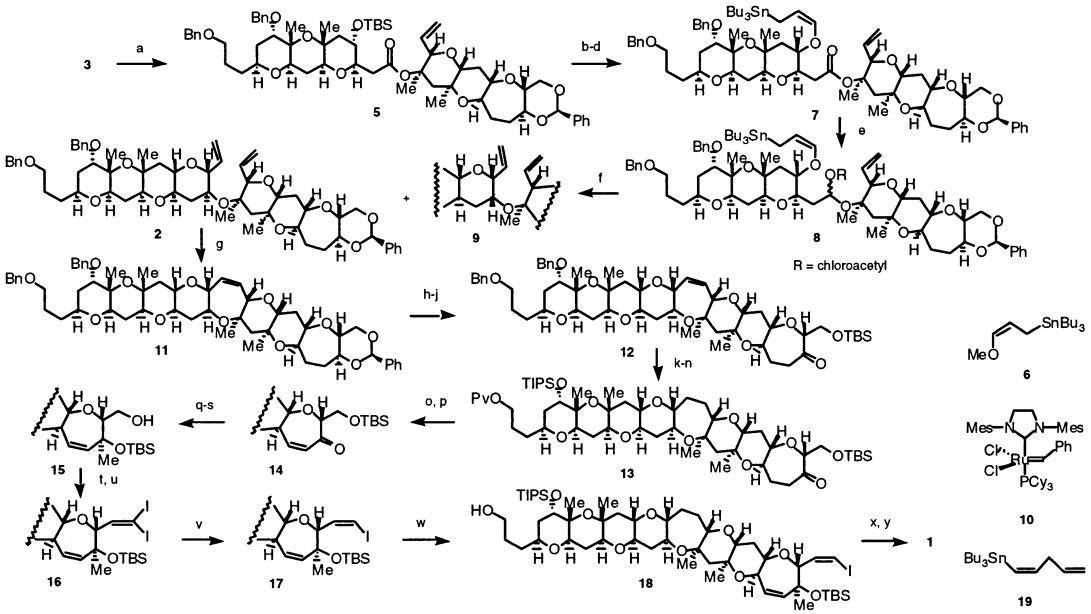
We have already succeeded in the stereoselective synthesis of the triene moiety via the Uenishi hydrogenolysis of dibromoalkene followed by a modified Stille coupling in a model study.[4c] However, the coupling reaction of *Z*-bromoalkenes was very slow. This problem prompted us to develop an efficient method for the construction of the triene side chain. After several unfruitful attempts, we found that *the reduction of diiodoalkenes with a Zn−Cu couple gave reactive Z-iodoalkenes in a highly stereoselective manner*.[15] Thus, PCC oxidation of **15** followed by treatment of the resulting aldehyde with CI_4 and PPh_3[16] gave the diiodoalkene **16** in 92% overall yield. Stereoselective hydrogenolysis of **16** was carried out by using a *Zn−Cu couple and AcOH in THF−MeOH* to give the *Z*-iodoalkene **17** as a single stereoisomer, which was then treated with DIBALH, furnishing **18** in quantitative yield. Deprotection of the bis-silyl ether **18** with SiF_4 proceeded smoothly to afford the corresponding triol.[17] Finally, the iodoalkene obtained was subjected to the modified Stille coupling with **19** to give gambierol (**1**) in 72% yield.[18] The synthetic gambierol exhibited physical and spectroscopic data identical to those reported previously.[3,5]

In conclusion, the convergent total synthesis of gambierol has been achieved using the intramolecular allylation of α-chloroacetoxy ether and subsequent ring-closing metathesis. The longest linear sequence leading to **1** was 66 steps with 1.2% overall yield, and the total number of steps was 102, while the synthesis by Sasaki and Tachibana gave an overall yield of 0.57% by 71 steps, with a total of 107 steps.[5] The present synthesis demonstrated that this methodology is efficient and practical for constructing polycyclic ether frameworks. Application of the present strategy to the synthesis of other marine natural products is in progress.

† Institute of Multidisciplinary Research for Advanced Materials.
‡ Graduate School of Science.

10.1021/ja028726d CCC: $25.00

Scheme 1 [a]



[a] (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, 40 °C, then **4**, DMAP, toluene, 40 °C, 94%; (b) TBAF, THF, room temperature, 99%; (c) **6**, CSA, CH_2Cl_2, room temperature; (d) HMDS, TMSI, CH_2Cl_2, 0 °C, 78% (two steps); (e) DIBALH, CH_2Cl_2, −78 °C, then $(CH_2ClCO)_2O$, DMAP, pyridine, −78 °C to room temperature, 88%; (f) BF_3·OEt_2, MS4A, CH_3CN, −40 to 0 °C, 87% (**2**:**9** = 2:1); (g) **10**, CH_2Cl_2, room temperature, 88%; (h) CSA, CH_2Cl_2−MeOH, 30 °C; (i) TBSCl, imidazole, CH_2Cl_2, 0 °C, 80% (two steps); (j) TPAP, NMO, MS4A, CH_2Cl_2, room temperature, 96%; (k) H_2, Pd−C, EtOAc, room temperature; (l) H_2, $Pd(OH)_2$−C, EtOAc, room temperature; (m) PvCl, DMAP, CH_2Cl_2, room temperature; (n) TIPSOTf, 2,6-lutidine, DMF, 65 °C, 80% (four steps); (o) LiHMDS, TMSCl, Et_3N, THF, −78 °C; (p) $Pd(OAc)_2$, CH_3CN, 92% (two steps); (q) MeMgI, toluene, −78 °C; (r) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature; (s) CSA, CH_2Cl_2−MeOH, 0 °C, 82% (three steps); (t) PCC, MS4A, CH_2Cl_2, room temperature; (u) CI_4, PPh_3, CH_2Cl_2, 0 °C, 92% (two steps); (v) Zn−Cu, AcOH, THF−MeOH, 0 °C; (w) DIBALH, CH_2Cl_2, −78 °C, 100% (two steps); (x) SiF_4, CH_2Cl_2−CH_3CN, 0 °C; (y) **19**, Pd_2dba_3·$CHCl_3$, P(furyl)$_3$, CuI, DMSO, 40 °C, 72% (two steps).

Acknowledgment. We thank Professor T. Yasumoto (Tohoku University) for providing the ^{1}H NMR spectrum of **1**, and Professor M. Hirama (Tohoku University) for supporting the measurement of MALDI TOF mass spectra. This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Schemes for the preparation of compounds **3** and **4**. Experimental procedures and characterization data for all new compounds reported in Scheme 1. Copies of ^{1}H NMR spectra for selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685−1698. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909.

(2) For recent reviews, see: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953−1980. (b) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589−607. (c) Mori, Y. *Chem.-Eur. J.* **1997**, *3*, 849−852. Also see: (d) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12630−12670.

(3) (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**, *39*, 97−100.

(4) (a) Kadota, I.; Park, C.-H.; Ohtaka, M.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6365−6368. (b) Kadota, I.; Kadowaki, C.; Yoshida, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6369−6372. (c) Kadota, I.; Ohno, A.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6373−6376. (d) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371−8375. (e) Sakamoto, Y.; Matsuo, G.; Matukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749−2752. (f) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919−2922. (g) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019−3033. (h) Fuwa, H.; Sasaki, M.; Tachibana, K. *Org. Lett.* **2001**, *3*, 3549−3552. (i) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6702−6703. (j) Kadota, I.; Kadowaki, C.; Park, C.-H.; Takamura, H.; Sato, K.; Chan, P. W. H.; Thorand, S.; Yamamoto, Y. *Tetrahedron* **2002**, *58*, 1799−1816. (k) Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3494−3498. (l) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 3562−3566.

(5) During our study, very recently the Sasaki and Tachibana group reported the first total synthesis of **1**. (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.*, in press.

(6) For the preparation of **3** and **4**, see Supporting Information.

(7) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(8) Kadota, I.; Sakaihara, T.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 3195−3198.

(9) Acetic anhydride was used in the original procedure, see: (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271−7274. (c) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198. (d) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219. (e) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679−4686.

(10) The reaction of the corresponding α-acetoxy ether gave the undesired isomer **9**, predominantly. Perhaps, the poor leaving ability of acetyl group, in comparison with chloroacetoxy group, would force the reaction course to proceed through the S_N2 pathway. The D ring of the desired isomer **2**, in which all of the substituents take an equatorial position, is more thermally stable than that of **9**. The details of the mechanism are under investigation. We appreciate a referee who pointed out the above problems, and we also thank Professor T. Oishi (Osaka University) and Professor M. Inoue (Tohoku University) for suggesting the use of the chloroacetyl group.

(11) For the determination of the stereochemistries of **2** and **9**, see Supporting Information.

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

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

(14) Feng, F.; Murai, A. *Chem. Lett.* **1992**, 1587−1590.

(15) The palladium-catalyzed hydrogenolysis of diiodoalkenes with Bu_3SnH was not selective, see: Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965−8975.

(16) Gavina, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Marco, J. A. *J. Chem. Res.* **1986**, 330−331.

(17) Corey, E. J.; Yi, K. Y. *Tetrahedron Lett.* **1992**, *33*, 2289−2290. The other attempts for desilylating the protected gambierol having the triene side chain, for example, the use of TBAF, TAS-F, and SiF_4, resulted in failure as reported by Sasaki, see ref 5.

(18) Fuji Silysia silica gel was used for the purification of **1**. Although the detail is not clear, the use of Kanto Chemical silica gel (neutral) caused partial isomerization of **1**. See Supporting Information.

JA028726D