Pergamon

Tetrahedron Letters 39 (1998) 6365–6368

TETRAHEDRON LETTERS

Synthesis of the AB Ring System of Gambierol

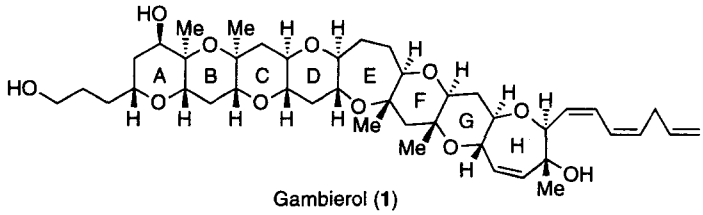
Isao Kadota,† Choul-Hong Park, Manabu Ohtaka, Nao Oguro, and Yoshinori Yamamoto*

Research Center for Organic Resources and Materials Chemistry, Institute for Chemical Reaction Science, and Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Received 15 April 1998; accepted 23 June 1998

Abstract: Synthesis of the AB ring system of gambierol (**1**) was achieved from 2-deoxy-D-ribose. The key steps were the stereoselective allylation of the aldehyde **6**, corresponding to the B ring, and the intramolecular hetero-Michael reaction of **9**.

Since 1981, a number of polycyclic ethers have been isolated from marine dinoflagellates.[1] Much attention has been paid to the synthesis of these compounds due to their unusual structures, biological activities, and rarity in nature.[2] Gambierol (**1**), which has a 6,6,6,6,7,6,6,7-polycyclic ether skeleton including 18 stereocenters and a triene side chain, was isolated from the cultured cells of *Gambierdiscus toxicus* by Yasumoto in 1993.[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.[2] Due to its limited availability from the natural source, the absolute configuration and the nature of the biological activity have not been established. In this paper, we report the stereocontrolled construction of the AB ring system of Gambierol (**1**) as a part of its total synthetic study.



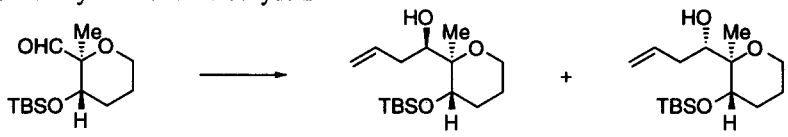
Gambierol (**1**)

First, the allylation of the aldehyde **2** was investigated as a model study for the stereoselective introduction of the hydroxy group on the A ring. Table 1 summarizes the results of the allylation of **2** under various conditions.[4] The best result was obtained from the reaction with allylmagnesium bromide in THF (entry 1). The desired stereoisomer **3** was produced as the major product in the ratio of 5:1. The use of less polar solvents such as ether and toluene decreased the stereoselectivity (entries 2 and 3). On the other hand, the reactions using allyltributyltin-Lewis acid combined systems gave predominantly the undesired isomer **4**. The stereochemistry of **3** was unambiguously determined by ^{1}H NMR analysis and NOE experiments of the

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01310-0

bicyclic derivative **5**, prepared by deprotection with TBAF followed by treatment with $PhCH(OMe)_2$/CSA (Scheme 1). Irradiation of the methyl protons (1.33 ppm) of **5** gave a significant enhancement (5.4%) of the resonances of the H_a and H_b protons (2.50-2.19 ppm). No NOE was observed between the methyl protons and the H_c proton. Based on these findings, we started a synthesis of the AB ring system of gambierol (**1**).

Table 1. Allylation of the aldehyde **2**[a]

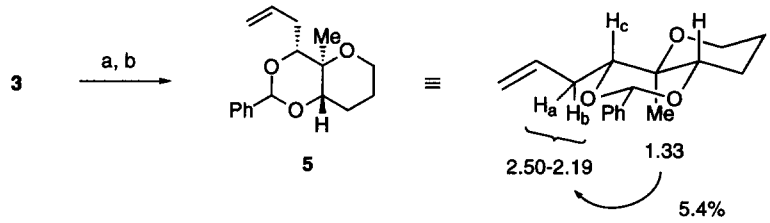


2 **3** **4**

entry	reagent	solvent	ratio (**3** : **4**)[b]	yield (%)[c]
1	allylmagnesium bromide	THF	5 : 1	91
2	allylmagnesium bromide	ether	3 : 1	78
3	allylmagnesium bromide	toluene	3 : 2	74
3	allyltributyltin/$TiCl_4$	CH_2Cl_2	1 : 4	-[d]
4	allyltributyltin/$BF_3 \cdot OEt_2$	CH_2Cl_2	1 : 5	-[d]

[a]All reactions were carried out with 1.2 equiv of the reagents at -78 ℃. [b]Determined by ^1H NMR analysis. [c]Isolated yields. [d]Not determined.

Scheme 1[a]

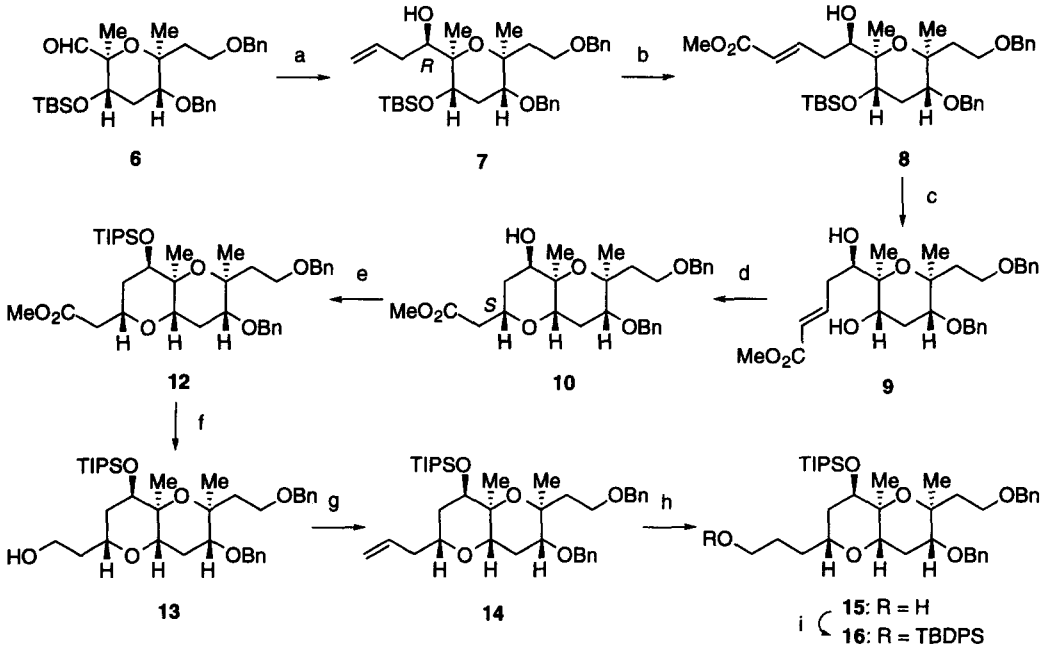


[a](a) TBAF, THF, 0 ℃, 100%; (b) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, 80%.

Reaction of the aldehyde **6**, prepared from 2-deoxy-D-ribose by the known procedure,[5] with allylmagnesium bromide in THF gave a 72:28 mixture of the corresponding homoallylic alcohol **7** and its epimer in 88% yield (Scheme 2). Oxidative cleavage of the double bond of **7** with OsO_4/$NaIO_4$ followed by Wittig reaction of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ afforded the α,β-unsaturated ester **8** in 63% yield. The TBS protective group of **8** was removed by the treatment with TBAF to give **9** in quantitative yield. The diol **9** obtained above was then subjected to the intramolecular hetero-Michael reaction.[6] The treatment of **9** with K_2CO_3[7] gave the desired and thermodynamically stable **10** as a major product in 75% yield with high stereoselectivity (9:1). The stereochemistry of the bicyclic system **10** was confirmed by the ^1H NMR analysis and NOE experiments on the corresponding acetate derivative **11** as shown in Figure 1.[8] The observed NOE (7.7%) between Me_a (1.31 ppm) and H_b (5.00 ppm) indicates the *trans* stereochemistry of the

methyl and the acetoxy group. Irradiation of H_c (4.17 ppm) gave an enhancement (12%) of the resonance at H_d (3.62 ppm), indicating the *cis* relationship of these protons.

Scheme 2[a]



[a](a) allylmagnesium bromide, THF, -78 °C, 88% (*R*:*S* = 72:28); (b) (i) OsO_4, $NaIO_4$, THF-H_2O, rt; (ii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, reflux, 63%; (c) TBAF, THF, 0 °C, 100%; (d) K_2CO_3, THF-MeOH, 40 °C, 75% (*S*:*R* = 90:10); (e) TIPSOTf, 2,6-lutidine, DMF, 70 °C, 96%; (f) $LiAlH_4$, ether, 0 °C, 88%; (g) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 °C to rt; (ii) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C, 90%; (h) 9-BBN, THF, rt, then H_2O_2, aq NaOH, rt, 90%; (i) TBDPSCl, imidazole, DMF, 40 °C, 93%.

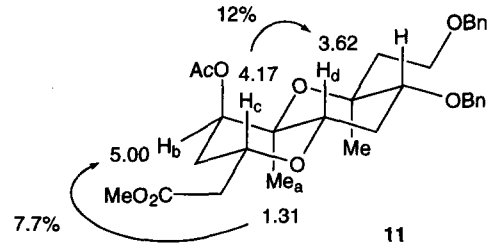


Figure 1. NOE experiments on the acetate **11**.

Introduction of the hydroxylated side chain was carried out in the following way (Scheme 2). The hydroxy group of **10** was protected as a TIPS ether using TIPSOTf/2,6-lutidine to give **12** in 96% yield. The undesired diastereomeric isomer formed in the cyclization step (**9** → **10**) was separated at this stage. Reduction of the ester group of **12** with $LiAlH_4$ gave the primary alcohol **13** in 88% yield. Swern oxidation

of **13** followed by Wittig reaction using $Ph_3P=CH_2$ afforded the olefinic compound **14** in 90% yield. Hydroboration of **14** with 9-BBN gave the primary alcohol **15** in 90% yield. Finally, the free hydroxy group was protected as a TBDPS ether using TBDPSCl/imidazole to give **16** in 93% yield.

Acknowledgement. This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan and a grant from Mitsubishi Chemical Company.

References

† Institute for Chemical Reaction Science

(1) For a recent review, see: 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.

(3) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361-362.

(4) For a recent review on the stereoselective allylation of aldehydes, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207-2293.

(5) (a) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517-4552. (b) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Reddy, K. B.; Defrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227-10238.

(6) For a recent example of the synthesis of cyclic ethers *via* the intramolecular hetero-Michael reaction, see: Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570-4583 and references cited therein.

(7) Tanaka, S.; Oguri, H.; Hishiyama, S.; Oishi, T.; Hirama, M. *The 70th Annual Meeting of the Chemical Society of Japan* **1996**. The conditions employed gave a better result than the usual conditions (NaH in THF) for this type of transformations.

(8) **11:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.24 (m, 10H), 5.00 (t, J = 2.9 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.45 (s, 2H), 4.44 (d, J = 11.5 Hz, 1H), 4.20-4.24 (m, 1H), 3.70 (s, 3H), 3.62 (dd, J = 12.7, 3.5 Hz, 1H), 3.59-3.52 (m, 1H), 3.51 (dd, J = 11.3, 4.6 Hz, 1H), 2.54 (dd, J = 15.4, 7.9 Hz, 1H), 2.39 (dd, J = 15.4, 4.9 Hz, 1H), 2.16 (ddd, J = 11.8, 4.0, 4.0 Hz, 1H), 2.01 (s, 3H), 2.00-1.71 (m, 6H), 1.31 (s, 3H), 1.28 (s, 3H).