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Stereocontrolled Synthesis of the A/B-Ring Fragment of Gambieric Acid B: Reassignment of the Absolute Configuration of the Polycyclic Ether Region

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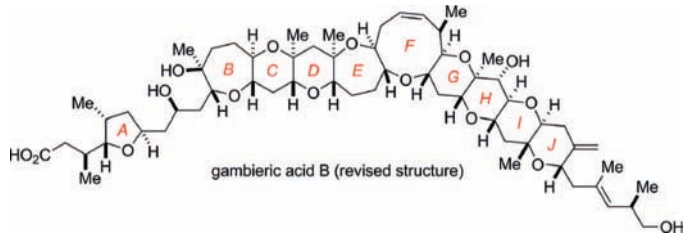
ABSTRACT



Stereocontrolled synthesis of the A/B-ring fragment of the originally assigned structure of gambieric acid B and its possible diastereomers has been accomplished. Detailed comparison of their ^{1}H and ^{13}C NMR data with those of the corresponding moiety of the natural product culminated in a stereochemical reassignment of the absolute configuration of the polycyclic ether region of gambieric acid B.

Gambieric acids A−D (GAA−GAD, Figure 1) are the prominent members of marine polycyclic ether natural products,[1,2] which were isolated from the cultured media of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*.[3,4] The structures of gambieric acids were determined by combining the results of extensive NMR studies, the modified Mosher method, and chiral fluorometric HPLC analysis. The relative stereochemistry of the C7−C11 acyclic portion, however, was correlated mainly on the basis of $^{3}J_{H,H}$ analysis and the NOESY and HMBC spectra. Therefore, unambiguous assignment of the relative configuration of the C1−C12 moiety have to be made with the aid of organic synthesis. These natural products exhibit extraordinarily potent antifungal activity against *Aspergillus niger* with a potency that is approximately 2,000 times greater than that of amphotericin B, whereas they are only weakly toxic toward mammalian cells.[5] It has also been reported that GAA enhances the cell concentration of *G. toxicus* in a dose-dependent manner with inhibition at higher concentrations, suggesting the possible role of GAA as an endogenous growth regulator of *G. toxicus*.[6] Moreover, Inoue et al. reported that GAA inhibits the binding of the tritiated

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(2) For recent reviews of the synthesis of polycyclic ethers, see: (a) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4347. (b) Evans, P. A.; Delouvrie, B. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 986. (c) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (d) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (e) Fuwa, H.; Sasaki, M. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 784.

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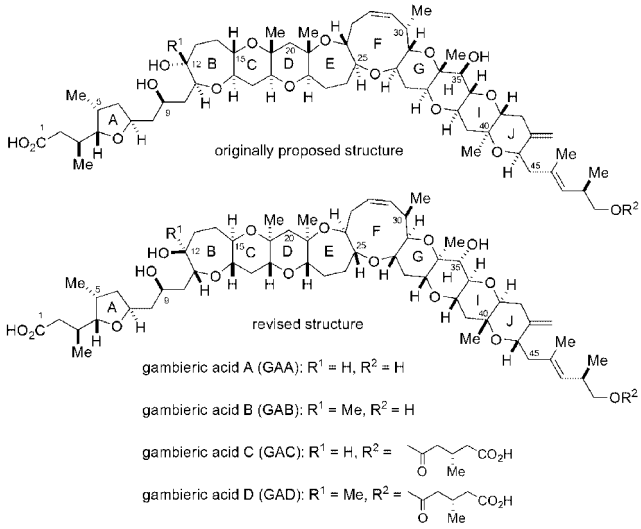


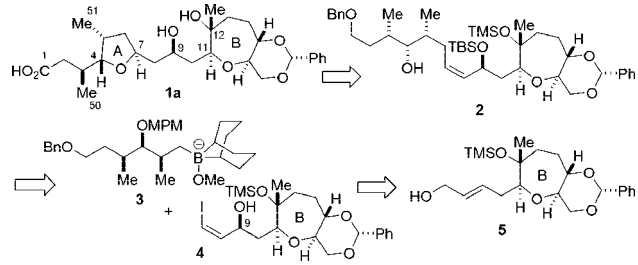
Figure 1. Proposed and revised structures of gambieric acids A−D.

brevetoxin-B derivative ([^{3}H]PbTx-3) to site 5 of the voltage-sensitive sodium channels of excitable membranes.[7] These intriguing biological aspects coupled with the synthetically formidable molecular architecture of these natural products have spurred the interest of the synthetic community.[8–12] In this Letter, we report a stereocontrolled synthesis and structure analysis of the A/B-ring fragment of GAB, which ultimately led to the reassignment of the absolute configuration of the polycyclic ether region of the originally proposed structure.

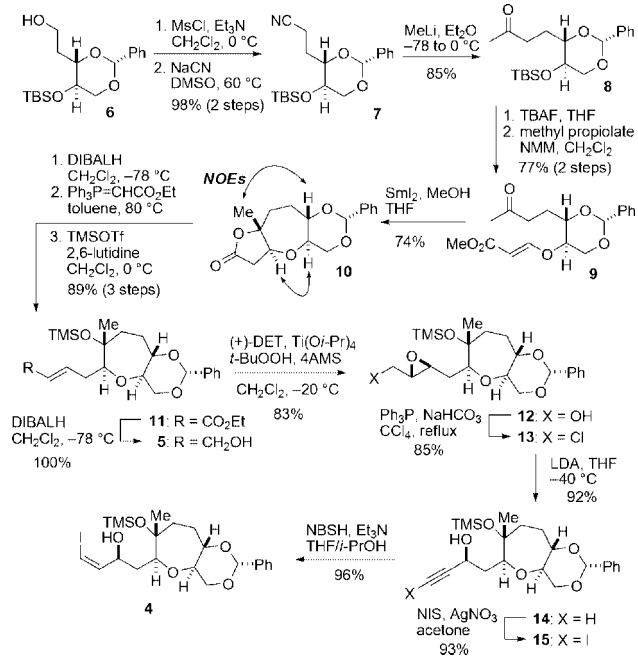
We envisaged that the A/B-ring fragment **1a** of GAB would be synthesized from alcohol **2** via a diastereoselective bromoetherification,[12] which in turn could be derived from alkylborate **3** and vinyl iodide **4** through *B*-alkyl Suzuki−Miyaura coupling[13] (Scheme 1). The synthesis of vinyl iodide **4** was planned from allylic alcohol **5** with Sharpless asymmetric epoxidation used as a key step to introduce the C9[14] stereocenter.

The synthesis of vinyl iodide **4** started with alcohol **6**,[15] which was converted to nitrile **7** via the corresponding mesylate (Scheme 2). Exposure of **7** to MeLi provided

Scheme 1. Synthetic Plan for the A/B-Ring Fragment **1a**



Scheme 2. Synthesis of Vinyl Iodide **4**



methyl ketone **8**, which was desilylated and subsequently reacted with methyl propiolate in the presence of NMM to afford β-alkoxyacrylate **9**. Upon treatment with SmI_2 in the presence of methanol,[16] reductive cyclization of **9** proceeded smoothly to yield tricyclic lactone **10** as a single stereoisomer. The newly generated stereocenters were established by NOE experiments as shown. DIBALH reduction of **10** followed by a Wittig reaction, and TMS protection of the remaining alcohol provided enoate **11**. After DIBALH reduction, the resultant allylic alcohol **5** was subjected to Sharpless asymmetric epoxidation using (+)-DET, yielding hydroxy epoxide **12** as a single stereoisomer. Hydroxy epoxide **12** was efficiently transformed into propargylic alcohol **14** via chloro-epoxide **13** by the Takano protocol.[17] Iodination of **14**, followed by diimide reduction[18] of the resultant iodoalkyne **15**, afforded vinyl iodide **4**.

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(12) Fuwa, H.; Suzuki, A.; Sato, K.; Sasaki, M. *Heterocycles* **2007**, *72*, 139.

(13) For reviews of Suzuki-Miyaura coupling, see: (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(14) The numbering of carbon atoms of all compounds in this paper corresponds to that of the natural product.

(15) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983.

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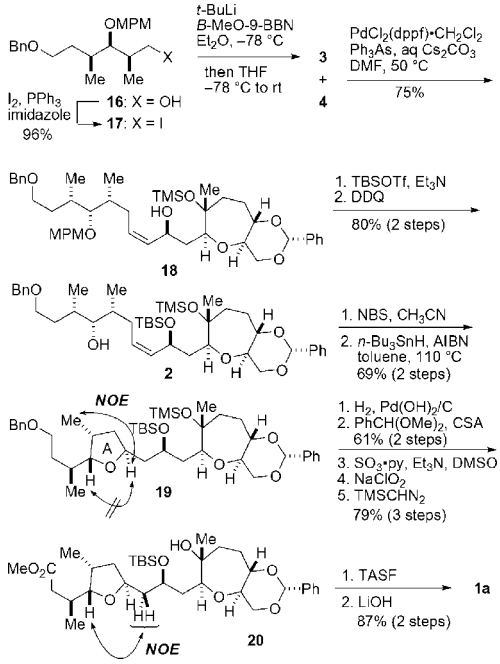
The key fragment assembly and the completion of the synthesis are illustrated in Scheme 3. A mixture of iodide

Scheme 3. Synthesis of A/B-Ring Fragment **1a**



17, obtained by iodination of alcohol **16**,[12] and *B*-MeO-9-BBN was treated with *t*-BuLi in diethyl ether.[19] The generated alkylborate **3** was coupled in situ with iodide **4** in the presence of a [$PdCl_2$(dppf)]/Ph_3As catalyst system and cesium carbonate in aqueous THF/DMF at 50 °C. This process provided the desired *cis*-olefin **18** in 75% yield. After silylation of the C9 hydroxy group, the MPM group was removed to give alcohol **2**. Exposure of **2** to NBS in CH_3CN resulted in a diastereoselective bromoetherification to provide a bromide,[20] which was immediately reduced under radical conditions to furnish the desired tricyclic compound **19** in an excellent overall yield. The stereochemistries at the C4, C5, and C7 positions were unambiguously confirmed by an NOESY experiment as shown. The desired isomer **19** would be derived from the transition state A (**TS-A**) after radical reduction, whereas **TS-B** would give the corresponding C7-epimer **19** (Figure 2). **TS-A** would be energetically more stable than **TS-B**, which suffers from the steric interaction between the C51 methyl group and the C7−C9 moiety.[21] Hydrogenolysis of **19** with a concomitant loss of the TMS

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(21) Our previous explanation[12] for the stereochemical outcome of the bromoetherification has turned out to be misleading, since this method could also be effective for the construction of the A-ring of compounds **1b**−**d**. For plausible rationales for the diastereoselectivity of the bromoetherifications in the synthesis of **1b**−**d**, see Supporting Information.

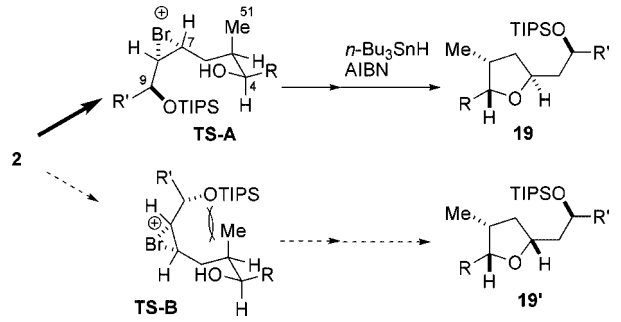

Figure 2. A plausible rationale for the stereochemical outcome of the bromoetherification of **2**.

group, followed by reprotection of the 1,3-diol moiety as its benzylidene acetal, gave an alcohol, which was oxidized to the corresponding acid and subsequently esterified to afford methyl ester **20**. Finally, removal of the TBS group by the action of TASF[22] and saponification provided the A/B-ring fragment **1a**.

The ^1H and ^{13}C NMR chemical shifts for the C1−C13 portion of **1a** (1:1 CD_3OD/C_5D_5N) were compared with those of the corresponding moiety of GAB (Table 1). It was

Table 1. ^1H and ^{13}C NMR Chemical Shift Deviations between GAB and Model Compounds **1a**−**d** (1:1 CD_3OD/C_5D_5N)[a]

	^1H NMR [$\Delta(\delta_N - \delta_S)$]				^{13}C NMR [$\Delta(\delta_N - \delta_S)$]			
position	**1a**	**1b**	**1c**	**1d**	**1a**	**1b**	**1c**	**1d**
2	0.06	0.06	0.10	0.09	0.6	0.6	0.6	0.7
	0.00	0.01	0.02	0.02				
3	0.00	0.01	0.01	0.02	0.0	0.2	0.1	0.2
4	0.02	0.01	0.08	0.00	0.3	0.0	0.3	0.0
5	0.04	0.05	0.08	0.06	0.1	0.3	0.1	0.2
6	−0.02	−0.01	0.02	−0.03	0.1	0.4	0.3	0.5
	−0.02	−0.09	0.02	−0.11				
7	**0.06**	**0.16**	**0.02**	**0.11**	**−0.5**	**−2.3**	**−0.2**	**−2.4**
8	**−0.15**	**−0.09**	**−0.04**	**−0.29**	**−1.7**	**−1.0**	**0.0**	**0.6**
	0.12	**−0.02**	**−0.04**	**0.00**				
9	**0.08**	**0.18**	**0.04**	**0.19**	**1.4**	**0.4**	**0.1**	**−1.3**
10	**0.09**	**0.12**	**−0.11**	**−0.09**	**0.5**	**0.8**	**0.3**	**0.4**
	0.10	**0.01**	**−0.11**	**−0.11**				
11	**−0.39**	**−0.38**	**−0.06**	**−0.08**	**1.4**	**1.7**	**0.1**	**0.3**
12					**0.3**	**0.3**	**0.2**	**0.2**
13	**−0.05**	**−0.05**	**−0.06**	**−0.01**	**0.3**	**0.3**	**0.6**	**1.2**
	−0.10	**−0.11**	**−0.05**	**−0.06**				
50	0.10	0.12	0.05	0.12	0.3	0.3	0.1	0.4
51	0.03	0.02	0.05	0.03	0.1	0.0	0.1	0.1
12Me	−0.02	−0.03	−0.01	−0.01	0.5	0.5	0.7	0.8

[a] ^1H and ^{13}C NMR spectra of natural GAB and **1a**−**d** were recorded at 400 MHz (100 MHz) and 600 MHz (150 MHz), respectively. Chemical shifts are reported in ppm relative to the internal residual solvent (^1H NMR, CD_2HOD 3.31 ppm; ^{13}C NMR, CD_3OD 49.8 ppm). δ_N and δ_S are chemical shifts of the natural product and synthetic model compounds, respectively.

observed that the ^1H and ^{13}C NMR chemical shifts of the C7−C11 moiety of **1a** significantly deviated from those of

GAB.[23] These spectroscopic discrepancies suggested that the original stereochemical assignment of GAB should be reexamined. According to Satake and co-workers, the relative stereochemical correlations between C7/C9 and C9/C11 were performed mainly on the basis of $^3J_{H,H}$ analysis and NOE data, and the absolute configuration of the C9 hydroxy group was established by the modified Mosher method.[4] Since unambiguous assignment of the relative configuration of the C7−C11 moiety deemed necessary, we decided to synthesize three possible diastereomers **1b**−**d** as potential candidates of the A/B-ring substructure of GAB (Figure 3).

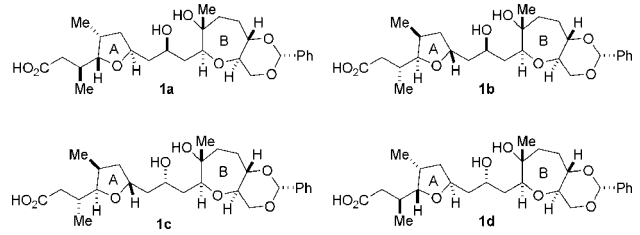

Figure 3. Possible diastereomeric compounds for the A/B-ring fragment of GAB.

Model compounds **1b**−**d** were synthesized in a manner similar to that described for **1a**.[24] Their ^{1}H and ^{13}C NMR chemical shifts measured in 1:1 CD_3OD/C_5D_5N are summarized in Table 1. Clearly, the ^{1}H and ^{13}C NMR chemical shifts of **1c** matched well those of GAB, while the other diastereomers displayed different spectroscopic properties. Furthermore, conformational analysis of **1c** based on $^3J_{H,H}$ values and the NOESY and HMBC spectra revealed that **1c** reproduces not only the relative stereochemistry but also the conformation of the C7−C11 moiety of the parent compound.[24] Because the C9 absolute configuration of **1c** is opposite to that of the natural product that had been determined unambiguously by the modified Mosher method, **1c** represents an enantiomer of the A/B-ring fragment of GAB. Thus, the present result indicates that the configuration of the polycyclic ether region of GAB should be revised such that it is the opposite of the original assignment. Overall, we revised the structure of GAB as shown in Figure 1.

In conclusion, we have described a stereocontrolled synthesis of the A/B-ring fragment of GAB, wherein the fragment assembly was efficiently accomplished by Suzuki−Miyaura coupling. However, the ^{1}H and ^{13}C NMR data of the A/B-ring fragment **1a** differed significantly from those of the C1−C13 moiety of GAB, respectively, indicating that the original stereochemical assignment should be reexamined. Fortunately, the high convergency of our synthetic route allowed us to elaborate three possible diastereomers **1b**−**d** efficiently. We finally found that the ^{1}H and ^{13}C NMR chemical shifts of **1c** matched well those of GAB, concluding that the absolute configuration of the polycyclic ether region of GAB should be revised such that it is the opposite of the original assignment. In view of biosynthesis, the structures of other gambieric acids should also be revised in a similar manner.

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Supporting Information Available: Synthetic schemes for compounds **1b**−**d**, detailed ^{1}H and ^{13}C NMR chemical shifts of compounds **1a**−**d**, conformational analysis of compound **1c**, and full experimental details and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Similarly, the ^{1}H and ^{13}C NMR chemical shifts of the C7-C11 moiety of **1a** in C_5D_5N differed from those of GAB in C_5D_5N. See Supporting Information for details.

(24) See Supporting Information for details.