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STEREOSELECTIVE SYNTHESIS OF THE AB-RING FRAGMENT OF GAMBIERIC ACID A†

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Abstract – Stereoselective synthesis of the AB-ring fragment of gambieric acid A has been accomplished, wherein (i) an acetylide–aldehyde coupling for fragment assembly and (ii) construction of the tetrahydrofuran A-ring via a diastereoselective bromoetherification were successfully employed as key transformations.

Gambieric acids A–D (**1**–**4**) are the prominent members of marine polycyclic ether natural products,[1,2] which were isolated from the cultured medium of the ciguatera causative dinoflagellate, *Gambierdiscus toxicus* (Figure 1).[3] The structures of gambieric acids A–D were determined by combining extensive NMR studies, the modified Mosher method, and chiral fluorimetric HPLC. These natural products exhibit exceeding antifungal activity against *Aspergillus niger* (approximately 2,000 times greater potency than amphotericin B), while they are only weakly toxic toward mammalian cells. These intriguing biological aspects coupled with synthetically daunting molecular architecture make these natural products highly rewarding synthetic targets for organic chemists. Consequently, several research groups,[4] including us,[5] have reported their efforts toward total synthesis of gambieric acids. Herein, we describe a stereoselective synthesis of the AB-ring fragment of gambieric acid A.

Our synthesis plan toward the AB-ring fragment (**5**) of gambieric acid A is illustrated in Scheme 1. We envisaged that the tetrahydrofuran A-ring could be constructed via haloetherification of hydroxy alkene **6**, which, in turn, would be accessible by an acetylide–aldehyde coupling of alkyne **7** and aldehyde **8**.

† This paper is dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

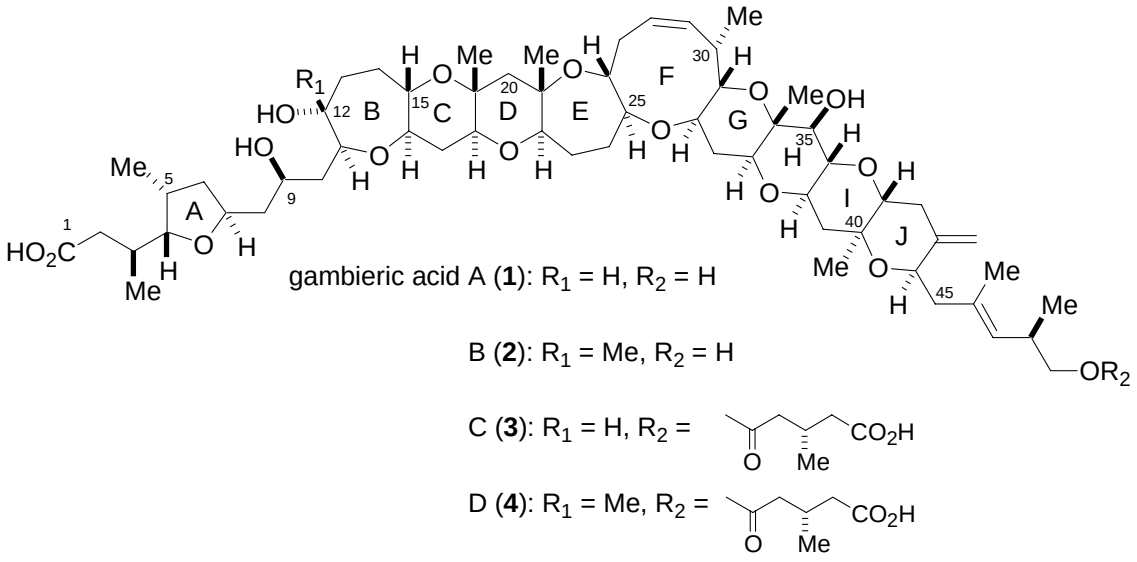
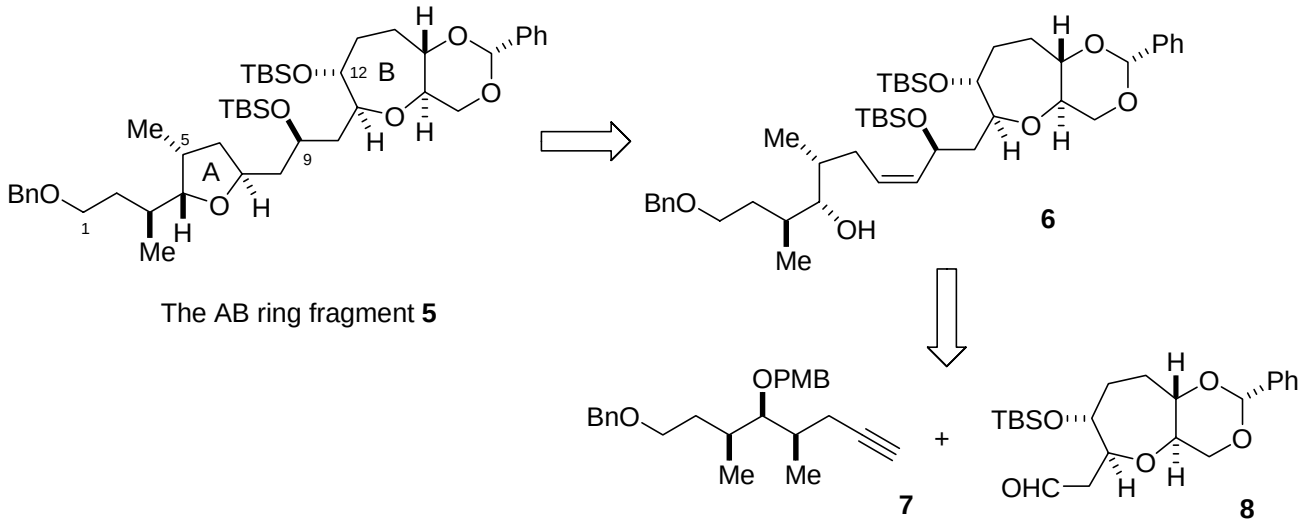
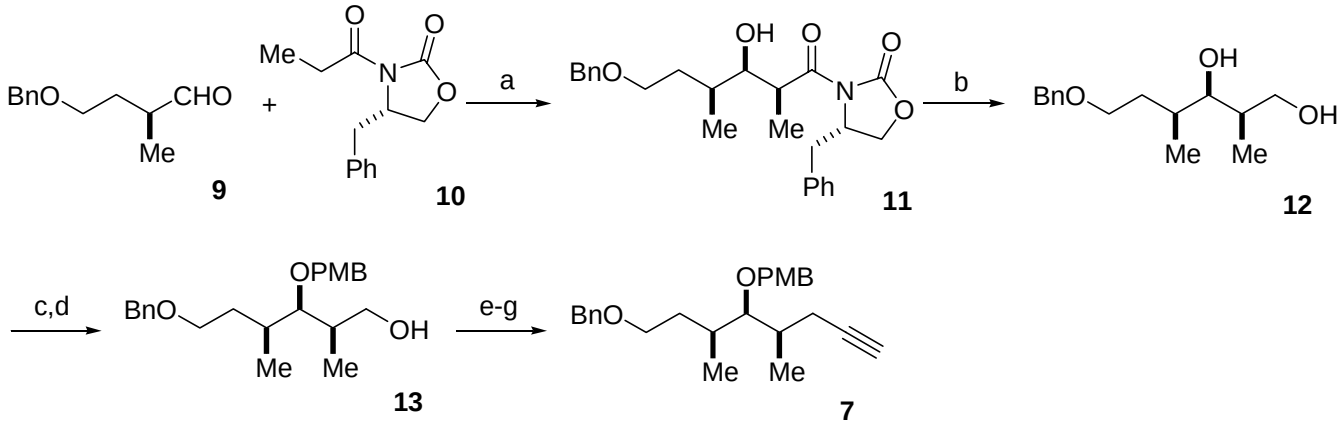


Figure 1. Structures of gambieric acids A-D.



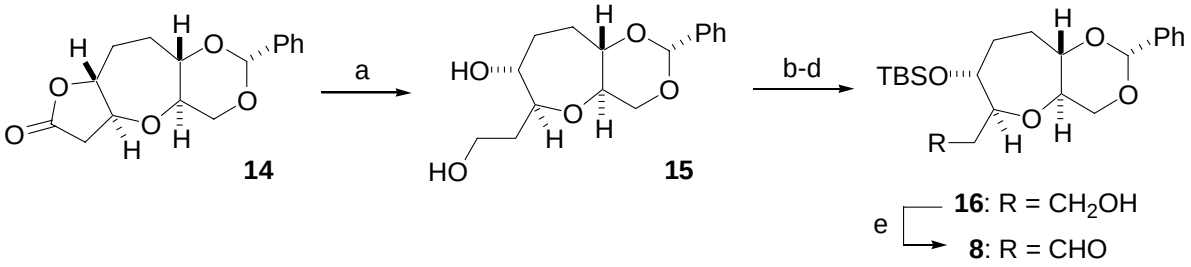
Scheme 1. Synthesis plan for the AB-ring fragment **5**.

The synthesis of alkyne **7** started with Evans *syn*-aldol condensation[6] of the known aldehyde **9**[7] with the boron enolate from oxazolidinone **10** to give alcohol **11** in 87% yield as a single stereoisomer (Scheme 2). After removal of the chiral auxiliary using $NaBH_4$ (THF/H_2O, 93%),[8] the resultant 1,3-diol **12** was protected as its *p*-methoxybenzylidene acetal, which was regioselectively reduced with DIBALH to afford primary alcohol **13** in 79% yield for the two steps. Triflation of **13** followed by reaction with lithium (trimethylsilyl)acetylide and desilylation under basic conditions gave alkyne **7** in 72% yield for the three steps.



Scheme 2. Synthesis of alkyne **7**. Reagents and conditions: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; then pH 7 buffer, H_2O_2, MeOH, rt, 87%; (b) $NaBH_4$, THF/H_2O, 0 °C to rt, 93%; (c) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, rt; (d) DIBALH, CH_2Cl_2, −78 to −40 °C, 79% (two steps); (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (f) 1-trimethylsilylacetylene, *n*-BuLi, HMPA, THF, −78 °C; (g) K_2CO_3, MeOH, rt, 72% (three steps).

The synthesis of aldehyde **8** is summarized in Scheme 3. The known lactone **14**[9] was reduced with $LiAlH_4$ to give diol **15**, which was efficiently converted to alcohol **16** in 88% overall yield via selective protection of the primary alcohol (PivCl, pyridine), masking of the remaining hydroxy group (TBSOTf, 2,6-lutidine), and reductive removal of the pivalate with DIBALH. Oxidation of alcohol **16** with SO_3·pyridine/DMSO afforded aldehyde **8** in 89% yield.



Scheme 3. Synthesis of aldehyde **8**. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C; (b) PivCl, pyridine, CH_2Cl_2, 0 °C to rt, 90% (two steps); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) DIBALH, CH_2Cl_2, −78 °C, 98% (two steps); (e) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C, 89%.

With the requisite fragments available, assembly of the fragments and construction of the A-ring were next executed (Scheme 4). Coupling of a lithium acetylide generated from **7** (3 equiv) and *n*-BuLi (2.8 equiv) with **8** (1 equiv) in THF at −78 °C provided an approximately 3:2 mixture of propargyl alcohols **17a,b** in 73% combined yield along with 13% of recovered **8** (84% yield based on recovered **8**). The use of excess molar amount of **7** was necessary to attain a practical level of conversion yield. Application of the modified Mosher method for determination of the newly generated C9 stereocenter of **17a,b** revealed that the major diastereomer **17a** possessed the desired stereochemistry as shown in Figure 2. Inversion of

the C9 stereochemistry of the undesired isomer **17b** was efficiently performed by Mitsunobu reaction[10] [(i) *p*-$NO_2C_6H_4CO_2H$, DEAD, Ph_3P; (ii) DIBALH], giving **17a** in 83% yield for the two steps. Hydrogenation of **17a** with Lindlar catalyst, protection of the hydroxy group with TBSOTf/2,6-lutidine, and removal of the PMB group with DDQ led to alcohol **6** in 81% yield for the three steps. Upon treatment of **6** with NBS in CH_3CN at room temperature,[11] diastereoselective bromoetherification took place smoothly to give bromide **18**, which was immediately reduced under radical conditions (*n*-Bu_3SnH, AIBN, 110 °C) to furnish the targeted AB-ring fragment **5**[12] along with its C7 epimer (4:1 dr, 87% combined yield for the two steps). These stereoisomers were readily separated by flash chromatography on silica gel. The stereochemistries of the C4, C5, and C7 of **5** were unambiguously confirmed by a ROESY experiment as shown in Figure 3. The stereochemical outcome of the bromoetherification can be rationalized by allylic 1,3-strain,[13] wherein the bulky C9 siloxy group acts as a directing element. Thus, we have completed a stereoselective synthesis of the AB-ring fragment **5** of gambieric acid A in just 13 steps from the known aldehyde **9**.

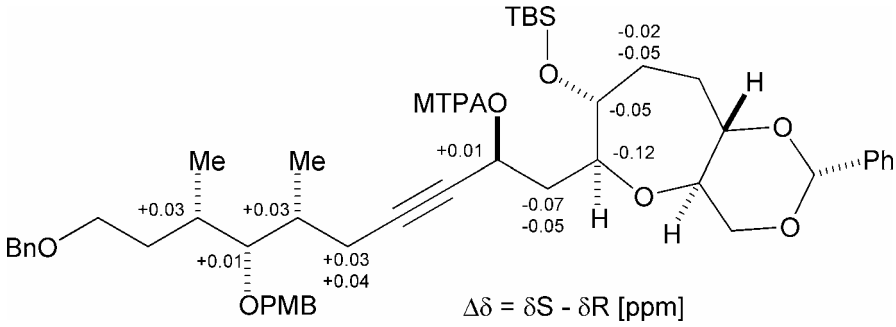
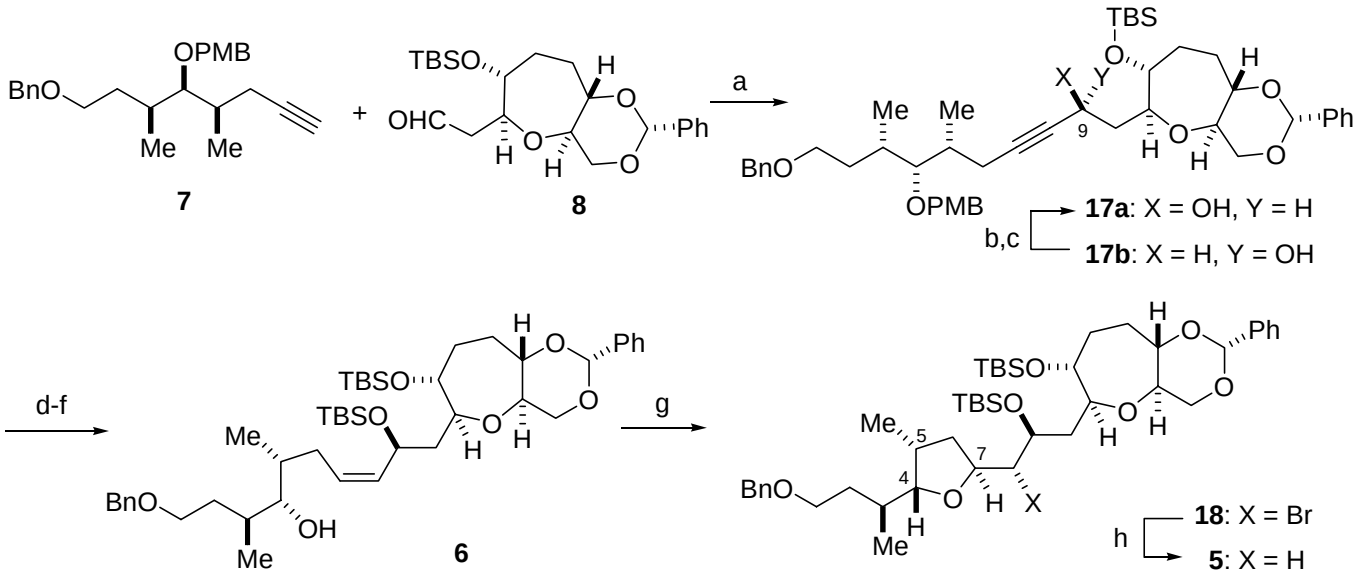


Figure 2. Determination of the stereochemistry of **17a** by the modified Mosher method.



Scheme 4. Synthesis of the AB-ring fragment **5**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 73% (13% of recovered **8**); (b) *p*-NO_2PhCO_2H, DEAD, Ph_3P, toluene, 0 °C; (c) DIBALH, CH_2Cl_2, −78 °C, 83% (two steps); (d) H_2, Lindlar's catalyst, cat. quinoline, 1-hexene/acetone, rt; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (f) DDQ, pH 7 buffer, CH_2Cl_2, rt, 81% (three steps); (g) NBS, CH_3CN, rt; (h) *n*-Bu_3SnH, AIBN, toluene, 110 °C, 87% (two steps, **5**:7-*epi*-**5** = 4:1).

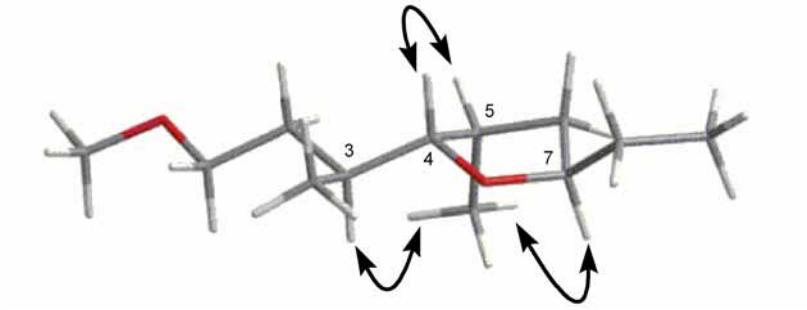


Figure 3. Establishment of the relative stereochemistry of **5**. Allows denote important ROEs. For clarity, only C1–C9 moiety is shown and the benzyl group was replaced with a methyl group.

In conclusion, we have accomplished a stereocontrolled synthesis of the AB-ring fragment of gambieric acid A based on an acetylide–aldehyde fragment assembly and a diastereoselective bromoetherification for the A-ring construction. Further efforts toward the total synthesis of gambieric acid A are in progress in our laboratory and will be reported in due course.

ACKNOWLEDGEMENTS

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12. Selected data for **5**: $[\alpha]_D^{24}$ −11.7 (*c* 0.90, $CHCl_3$); IR (film) 2929, 2855, 1461, 1376, 1252, 1053, 835, 774, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.68—7.66 (m, 2H), 7.31—7.30 (m, 2H), 7.19—7.08 (m, 6H), 5.42 (s, 1H), 4.52 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.35 (d, *J* = 12.5 Hz, 1H), 4.31 (d, *J* = 12.5 Hz, 1H), 4.29—4.22 (m, 2H), 3.95—3.90 (m, 2H), 3.74 (m, 1H), 3.58 (dd, *J* = 11.0, 11.0 Hz, 1H), 3.46—3.42 (m, 2H), 3.38—3.36 (m, 2H), 2.34 (m, 1H), 2.03 (m, 1H), 1.93—1.89 (m, 2H), 1.82 (m, 1H), 1.76—1.64 (m, 5H), 1.60—1.50 (m, 3H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.17 (m, 1H), 1.05 (s, 9H), 0.95 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.24 (s, 3H), 0.21 (s, 3H), 0.05 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.4, 139.1, 128.7, 128.5 (×2), 128.2 (×2), 127.61 (×2), 127.59, 126.9 (×2), 101.2, 85.7, 83.0, 82.2, 76.2, 73.1, 73.0, 72.7, 70.2, 68.1 (x 2), 46.7, 44.6, 41.7, 35.3, 33.5, 31.6, 26.8, 26.5, 26.3 (×3), 26.0 (×3), 18.4, 18.2, 17.5, 14.0, −4.1, −4.2, −4.58, −4.64; HRMS (ESI) calcd for $C_{45}H_{74}O_7Si_2Na$ [$(M+Na)^+$] 805.4871, found 805.4868.
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