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Synthetic studies towards gambierol. Part 1: Synthesis of the AB ring segment

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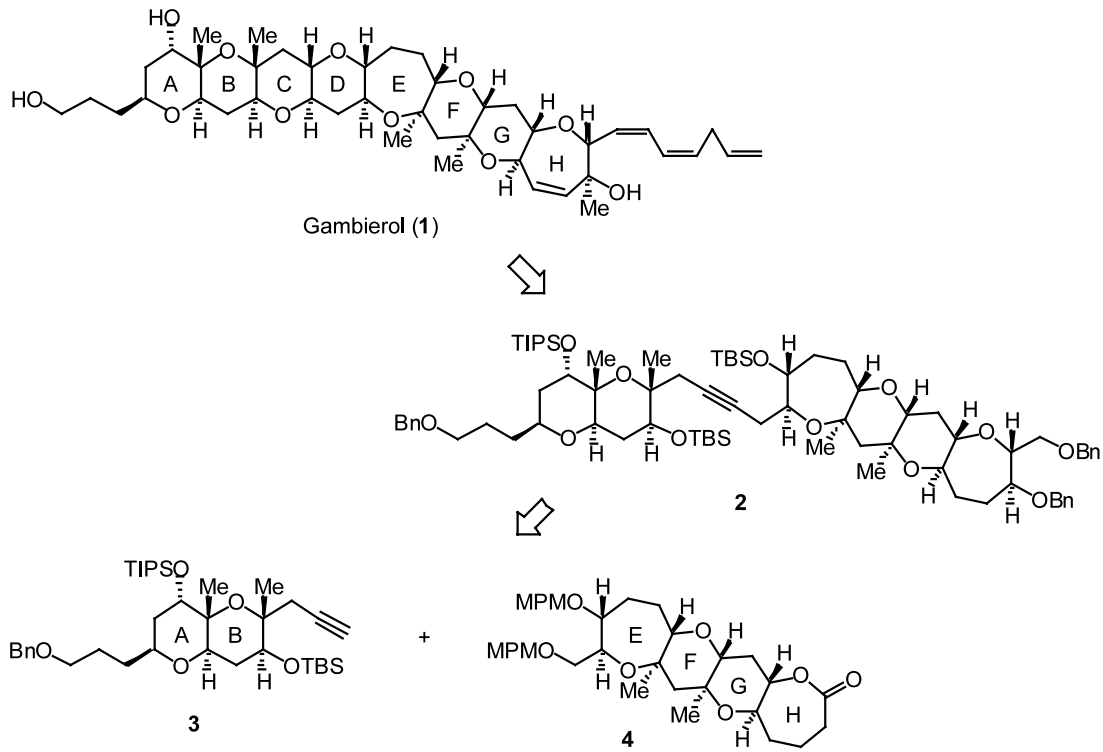
Abstract—The AB ring segment of gambierol (**1**) was synthesized from 2-deoxy-D-ribose in 23 steps. The key steps were Brown's asymmetric allylboration of the aldehyde **5** and the intramolecular hetero-Michael reaction of **7**.

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.[1] The compound shows significant 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] In the course of our



Scheme 1.

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synthetic effort towards gambierol, we synthesized the AB ring segment in 1998,[3] based on the absolute stereochemistry proposed by Yasumoto and co-workers in 1993.[1] However, later on in 1999, they revised the absolute stereochemistry;[2] it is now believed to be the opposite to that reported in 1993. Accordingly, we undertook to synthesize the AB ring segment having the correct absolute stereochemistry. Scheme 1 illustrates our new synthetic strategy for the convergent synthesis of **1**. The polycyclic ether framework of **1** would be constructed from **2** via oxidation of the C–C triple bond to an α-diketone, selective removal of the TBS protective groups, and subsequent reductive cyclization of the resulting hydroxy ketone.[4] Retrosynthetic disassembly of the alkyne **2** based on a *retro*-acetylide–triflate coupling furnished the AB ring segment **3** and the EFGH ring segment **4**.[5] In this paper, we wish to report the stereocontrolled synthesis of the natural AB ring segment **3** as part of the total synthetic study of **1**.

Protection of the known starting material **5**[6] with TBSCl followed by ozonolysis gave the aldehyde **6** in 99% yield (Scheme 2). Brown's asymmetric allylboration of **6** using allyldiisopinocampheylborane derived from (+)-pinene afforded the homoallylic alcohol **7** as the sole product in 92% yield.[7,8] Deprotection of the silyloxy group of **7** using TBAF and ozonolysis followed by Wittig reaction gave the α,β-unsaturated ester **8** in 94% yield. The cyclization precursor **8** was then subjected to an intramolecular hetero-Michael reaction. Thus, treatment of **8** with 20 mol% of DBU in refluxing toluene gave a 12:1 mixture of the desired bicyclic compound **9** and its diastereoisomer in 78% combined yield.[9] The stereochemistry of the major product **9** was unambiguously confirmed by NOE experiments on the corresponding acetate derivative as shown in Fig. 1.

We next examined the chain elongation and introduction of an alkynyl group as shown in Scheme 3. Protection of the hydroxy group of **9** with TIPSOTf followed by reduction of the ester group of **10** with $LiAlH_4$ gave the alcohol **11** in 94% yield. One carbon elongation of the hydroxymethyl group of **11** was achieved in the following way. Swern oxidation and subsequent Wittig reaction of the resulting aldehyde with $Ph_3P{=}CH_2$ gave the corresponding one carbon elongated olefin, which was converted to the alcohol **12** through hydroboration in 85% yield. Benzyl protection of the hydroxy group of **12** followed by removal of the benzylidene acetal using catalytic CSA in MeOH furnished the diol **13** in 99% yield. Protection of **13** as a bis TBS ether followed by selective deprotection of the primary silyloxy group gave **14** in 76% yield. Swern oxidation, Wittig reaction, and hydroboration afforded the alcohol **15** in 72% yield. Conversion of **15** to the alkyne **17** was performed by oxidation with $SO_3{\cdot}py/DMSO/Et_3N$, reaction with CBr_4/PPh_3, followed by treatment of the resulting dibromoolefin **16** with *n*-BuLi.[10,11] The yield of **17** from **15** was 96%.

In conclusion, the synthesis of the AB ring segment, having absolute stereochemistry corresponding to natural gambierol **1**, was achieved from 2-deoxy-D-ribose. Brown's asymmetric allylboration and the intramolecular hetero-Michael reaction were successfully applied to the construction of the A ring moiety.

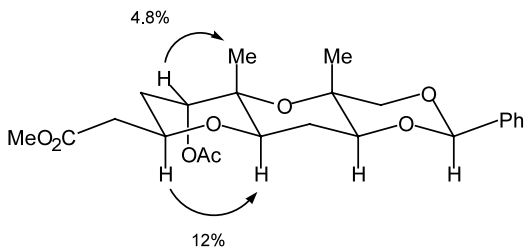
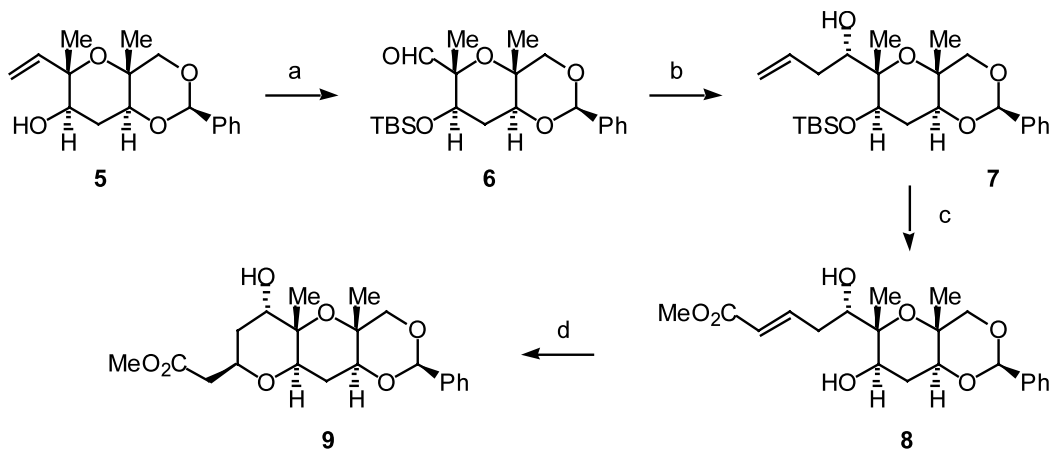
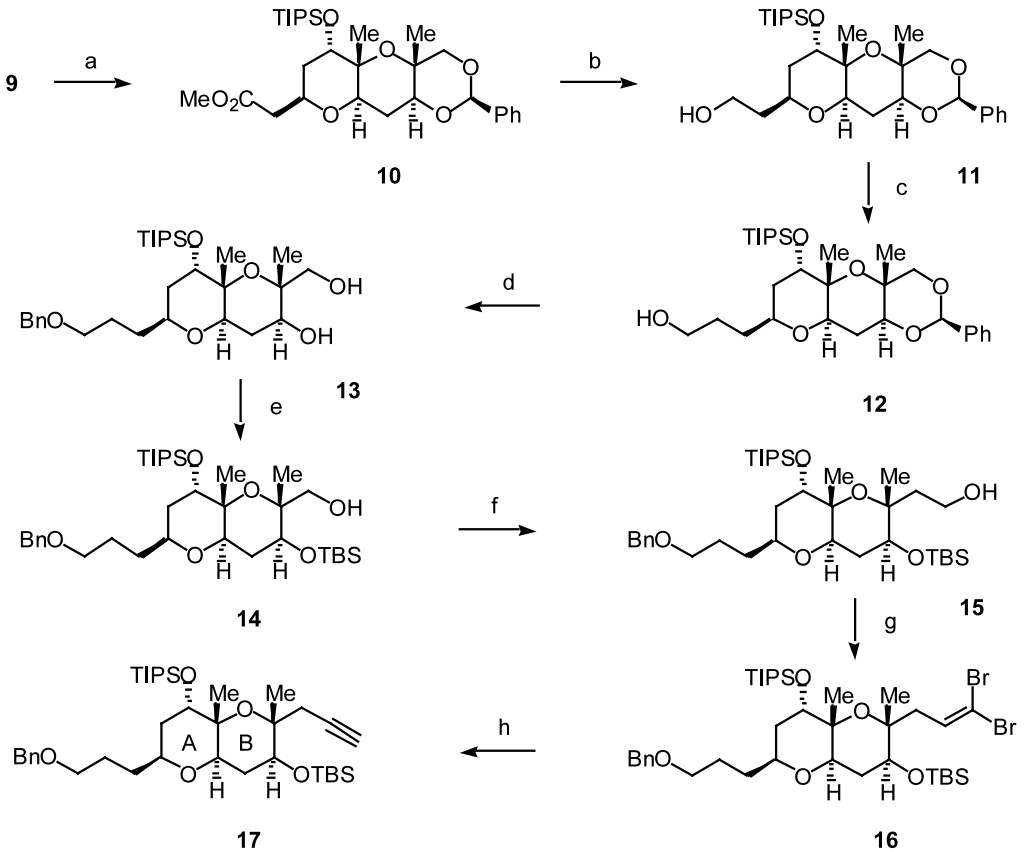


Figure 1. Observed NOEs are shown by arrows.



Scheme 2. (a) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 40°C, 100%; (ii) O_3, CH_2Cl_2–MeOH, −78°C, then PPh_3, −78°C to rt, 99% (two steps); (b) ^{d}Ipc$_2$B-allyl, ether, −78°C; H_2O_2, NaOH, rt, 92%; (c) (i) TBAF, THF, rt, 100%; (ii) O_3, CH_2Cl_2–MeOH, −78°C, then PPh_3, −78°C to rt, 99%; (iii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt, 95%; (d) DBU, toluene, 110°C, 78% (92:8).



Scheme 3. (a) TIPSOTf, 2,6-lutidine, DMF, 60°C, 98%; (b) $LiAlH_4$, ether, 0°C, 96%; (c) (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% (two steps); (iii) $(c\text{-Hex})_2BH$, 0°C, then 30% H_2O_2, 3N NaOH, 0°C to rt, 94%; (d) (i) BnBr, KH, THF, 60°C; (ii) CSA, MeOH, rt, 99% (two steps); (e) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt; (ii) CSA, MeOH–CH_2Cl_2, rt, 76% (two steps); (f) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, −78°C to rt; (ii) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 40°C, 97% (two steps); (iii) $BH_3{\cdot}SMe_2$, 0°C, then 30% H_2O_2, 3N NaOH, 0°C to rt, 74%; (g) (i) $SO_3{\cdot}$py, DMSO, Et_3N, CH_2Cl_2, 0°C; (ii) CBr_4, PPh_3, CH_2Cl_2, 0°C, 97% (two steps); (h) *n*-BuLi, THF, −78°C, 99%.

Acknowledgements

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11. Compound **17**: colorless oil; $[\alpha]_D^{24}$ +49.0 (*c* 0.50, $CHCl_3$); IR (neat) 3313, 2950, 2120, 1463, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5H), 4.48 (s, 2H), 3.91 (s, 1H), 3.83 (m, 1H), 3.76 (dd, $J=12.1$, 4.2 Hz, 1H), 3.46 (m, 3H), 2.45 (dd, $J=16.3$, 2.8 Hz, 1H), 2.45 (dd, $J=16.3$, 2.8 Hz, 1H), 2.10 (d, $J=16.2$ Hz, 1H), 1.90 (t, $J=2.0$ Hz, 1H), 1.88–1.38 (m, 7H), 1.32 (s, 3H), 1.26 (s, 3H), 1.10–0.95 (s, 21H), 0.85 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 128.3, 127.6, 127.5, 81.7, 77.7, 75.0, 74.2, 73.2, 72.9, 71.3, 69.7, 65.8, 38.4, 32.9, 32.3, 31.6, 31.4, 25.9, 25.7, 22.6, 21.4, 19.2, 18.4, 18.3, 17.8, 15.2, 14.1, 12.5, −3.9, −5.1; HRMS (EI) calcd for $C_{35}H_{59}O_5Si_2$ ($M-C_3H_7$) 615.3901, found 615.3905.