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# Synthesis of the A ring segment of gambieric acid

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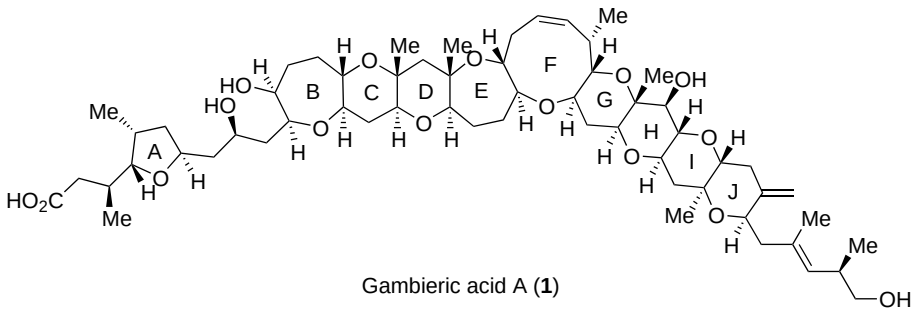
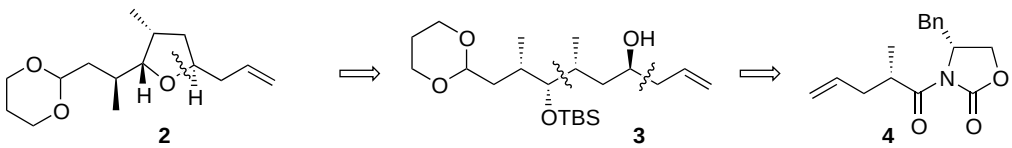
**Abstract**—The A ring fragment of gambieric acids was stereoselectively synthesized based on an Evans' asymmetric alkylation, Brown's asymmetric crotyl-, allylboration and an intramolecular $S_N2$ reaction. 

Gambieric acids A–D, potent antifungal substances isolated from the culture medium of the marine dinoflagellate *Gambierdiscus toxicus* in 1992, have *trans*-fuzed polycyclic ether skeletons including five-, six-, seven-, and nine-membered ether rings.[1] Their unprecedented antifungal activities against *Aspergillus niger* were 2000 times greater than that of amphotericin B, a widely used antifungal agent. The low toxicity of gambieric acids against mice and cultured mammalian cells points to the potential of the acids as antifungal drugs. Very recently, the absolute configurations were determined by NMR analysis.[2] In this paper, we report the stereoselective synthesis of the A ring segment of gambieric acids.

Our synthetic strategy is illustrated in Scheme 1. The tetrahydrofuran ring of the target molecule **2** is broken by the intramolecular $S_N2$ reaction leading to **3**. It was thought that the cyclization precursor **3** would be synthesized by Brown's asymmetric crotyl- and allylboration from the known starting material **4**, which can be prepared by Evans' asymmetric alkylation.

Ozonolysis of **4**,[3] prepared by Evans' stereoselective alkylation,[4] followed by the treatment of the resulting aldehyde with 1,3-propanediol in the presence of *p*-toluenesulfonic acid gave the acetal **5** in 93% yield (Scheme 2). Removal of the chiral auxiliary was performed using $LiBH_4$ to give the alcohol **6** in 90% yield.[5]




**Scheme 1.** Retrosynthesis of the A ring segment **2**.

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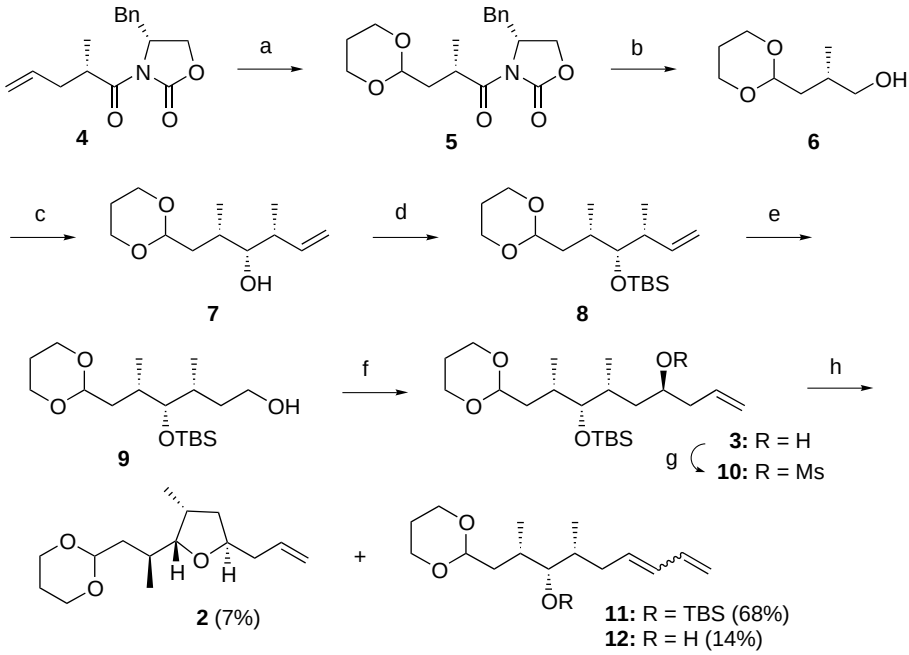
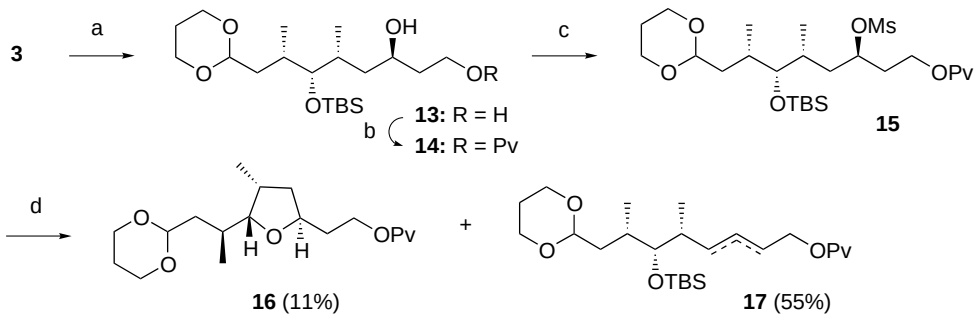


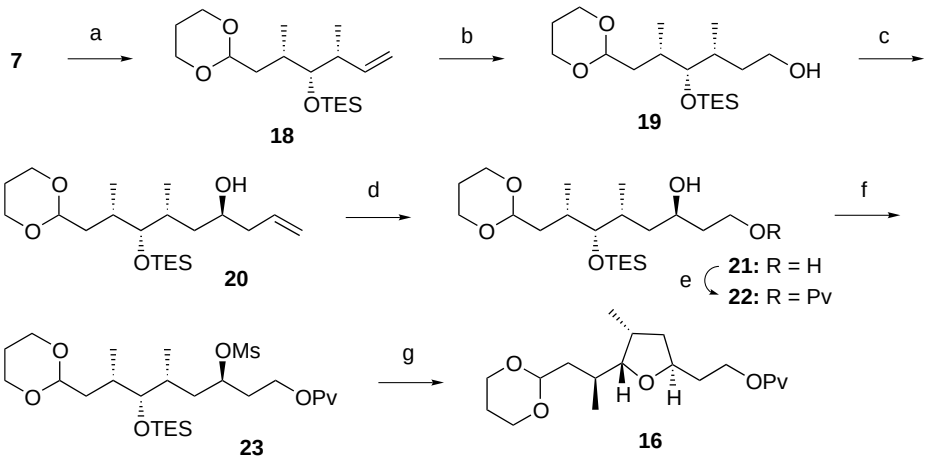

**Scheme 2.** (a) (i) $O_3$, MeOH, −78°C; $Me_2S$, −78°C to rt; (ii) 1,3-propanediol, *p*-TsOH, benzene, reflux, 93%; (b) $LiBH_4$, $H_2O$, ether, 0°C to rt, 90%; (c) (i) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78°C; $Et_3N$, −78°C to rt; (ii) $^d$Ipc$_2$B-(*Z*)-crotyl, THF, −78°C; $H_2O_2$, NaOH, 65°C, 72%; (d) TBSCl, 2,6-lutidine, $CH_2Cl_2$, 0°C to rt, 100%; (e) 9-BBN, THF, rt; $H_2O_2$, NaOH, rt, 91%; (f) (i) Dess–Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, rt, 84%; (ii) $^d$Ipc$_2$B-allyl, ether, −78°C; $H_2O_2$, NaOH, rt, 88%; (g) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C to rt, 100%; (h) TBAF, THF, rt.

Swern oxidation of **6** gave the corresponding aldehyde, which was subsequently treated with (*Z*)-crotyldiisopinocamphenylborane derived from (+)-pinene, to afford the homoallylic alcohol **7** in 72% yield with high diastereoselectivity.[6] No other stereoisomers were detected in this reaction. Protection of the hydroxy group with TBSCl and subsequent hydroboration of the resulting TBS ether **8** using 9-BBN gave the primary alcohol **9** (91% from **7**). Dess–Martin oxidation of **9** followed by Brown's asymmetric allylboration gave the alcohol **3** in 80% yield with high diastereoselectivity (16:1).[7] The secondary alcohol **3** was converted to the mesylate **10**, which was then subjected to a one-pot desilylation–cyclization reaction.[8] Unfortunately, treatment of **10** with TBAF at room temperature gave the cyclization product **2** in only 7% yield along with large amounts (82%) of the dienes **11** and **12**. Elimination of the homoallylic mesylate **10** giving the conjugated diene would appear to be faster than desilylation under these basic conditions.

Since several attempts at improving the yield of **2** resulted in failure,[9] we next examined the preparation of the cyclization substrate **15** which has a protected hydroxy group, instead of an olefin, at the terminus of the carbon chain (Scheme 3). Ozonolysis of **3**, a reductive workup with $Me_2S$, and treatment of the resulting aldehyde with $NaBH_4$ gave the diol **13** in 82% yield. Selective protection of the primary hydroxy group with PvCl/pyridine gave **14** in 71% yield. The secondary alcohol of **14** was converted to the mesylate **15** in quantitative yield. The cyclization precursor **15** was treated with TBAF to give **16** in 11% yield. A mixture of olefins **17** was obtained as the major product. The




**Scheme 3.** (a) $O_3$, MeOH, −78°C; $Me_2S$, −78 to 0°C; $NaBH_4$, 0°C to rt, 82%; (b) PvCl, pyridine, $CH_2Cl_2$, 0°C to rt, 71%; (c) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C to rt, 89%; (d) TBAF, THF, rt to 65°C.




**Scheme 4.** (a) TESCl, 2,6-lutidine, $CH_2Cl_2$, 0°C to rt, 100%; (b) 9-BBN, THF, rt; $H_2O_2$, NaOH, rt, 86%; (c) (i) Dess–Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, rt, 84%; (ii) $^d$Ipc$_2$B-allyl, ether, −78°C; $H_2O_2$, NaOH, rt, 95%; (d) $O_3$, MeOH, −78°C; $Me_2S$, −78 to 0°C; $NaBH_4$, 0°C to rt, 71%; (e) PvCl, pyridine, $CH_2Cl_2$, 0°C to rt, 56%; (f) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C to rt, 100%; (g) TBAF, THF, rt, 84%.

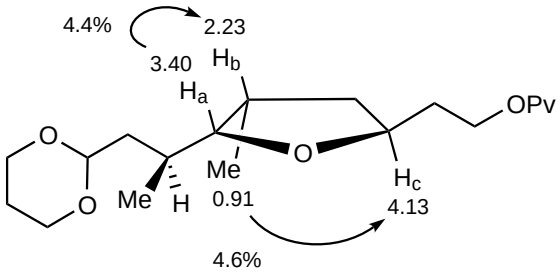



**Figure 1.** NOE experiments on **16**.

above trials indicated that the TBS ether having two methyl groups on neighboring carbons was quite stable under the usual deprotection conditions.

Scheme 4 shows our final synthetic approach using a TES ether as the protective group instead of TBS. The alcohol **7** was converted to the cyclization precursor **23** in good yield by similar procedures to those described in Schemes 2 and 3. Treatment of **23** with TBAF at room temperature promoted the cleavage of the TES ether smoothly and the subsequent intramolecular $S_N2$ reaction to give the tetrahydrofuran **16** as the sole product in 84% yield.

The stereochemistry of **16** was confirmed by $^1$H NMR analysis and NOE experiments as shown in Fig. 1. The observed NOE (4.4%) between $H_a$ (3.40 ppm) and $H_b$ (2.23 ppm) indicates the *cis* relationship of these protons. Irradiation of the methyl protons (0.91 ppm) gave a significant enhancement (4.6%) of the resonance of the $H_c$ proton (4.13 ppm). No NOE was observed between the $H_a$ and $H_c$ protons.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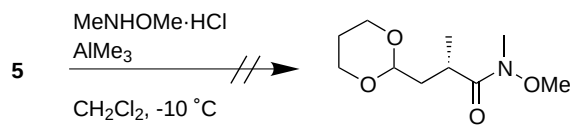
5. Conversion to the corresponding Weinreb amide failed. Decomposition of the substrate **5** took place under these conditions.

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9. No reaction took place with TBAF in the presence of acetic acid. The use of HF·pyridine or $SiF_4$ caused decomposition of the starting material.