Stereocontrolled Synthesis of the DEFG-ring Skeleton of Gambieric Acids

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A stereocontrolled entry to the DEFG-ring skeleton of gambieric acids, potent antifungal polycyclic ether natural products, has been developed based on the Suzuki–Miyaura coupling as the fragment assembly process and the use of an oxepane as a template for controlling the C25 stereogenic center.

Gambieric acids A–D (GAA–GAD, Figure 1) are marine polycyclic ether natural products isolated from the ciguatera causative dinoflagellate *Gambierdiscus toxicus* by Nagai, Yasumoto, and co-workers.[1] Their extraordinary complex molecular architecture coupled with highly potent antifungal activity make GAs formidable synthetic targets for organic chemists.[2–6] We have recently reassigned the absolute configuration of the polycyclic ether domain of GAs.[2e,2f] Our group has previously described a convergent synthesis of the nonacyclic polyether core of GAA and GAC.[2a–2c] However, our previous strategy suffered from low material throughput mainly due to the lack of stereocontrol at the C25 stereogenic center. Herein, we report a new strategy for the synthesis of the DEFG-ring skeleton of GAs. Our new strategy involves the Suzuki–Miyaura coupling as the fragment assembly process and utilizes an oxepane as a template for controlling the C25 stereogenic center.

Our synthesis plan toward the DEFG-ring skeleton **1** is illustrated in Scheme 1. As reported previously, we planned to construct the F-ring via a ring-closing metathesis[7] of diene **2**, which could be traced back to ester **3** via formation of the E-ring by lactonization. We envisioned that elaboration of ester **3** would be achieved by an oxidative cleavage of α-hydroxy ketone **4**. In turn, **4** could be derived from endocyclic enol ether **5** with simultaneous incorporation of the C25 stereogenic center via a substrate-controlled stereoselective hydroboration. Finally, **5** was planned to be derived from the Suzuki–Miyaura coupling[8] of an alkylborane generated from olefin **6** and enol phosphate **7**.

The synthesis of olefin **6** commenced with the known alcohol **8**[9] (Scheme 2). Protection of **8** as its TMS ether was followed by reduction to give alcohol **9**. Dehydration of **9** via a selenide

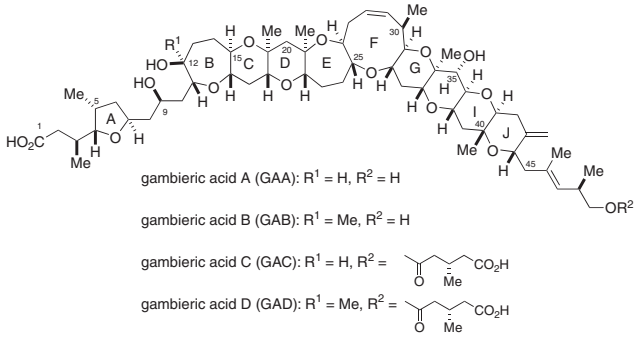
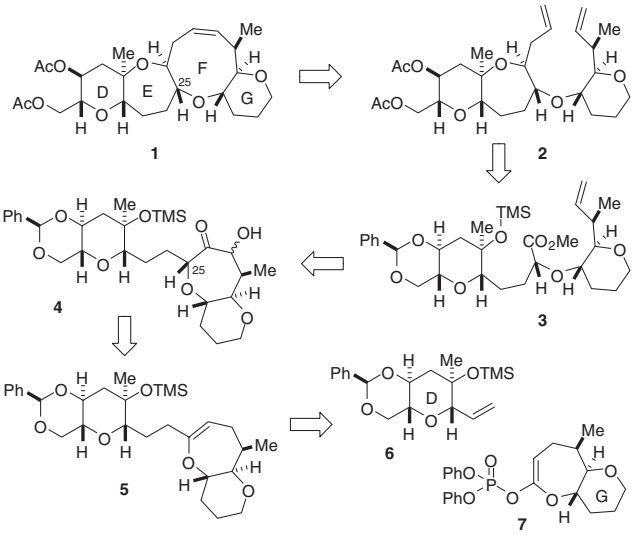
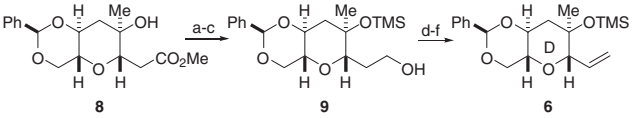


Figure 1. Structures of gambieric acids (GAs).



Scheme 1. Our new strategy for the synthesis of the DEFG-ring skeleton of GAs.

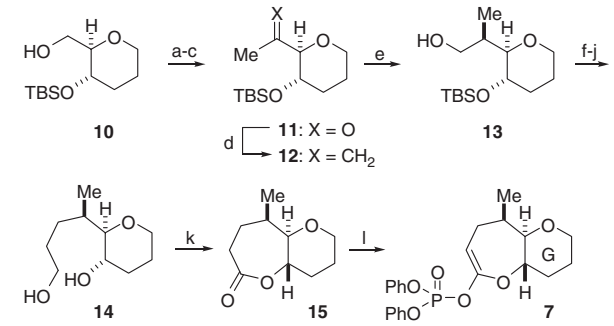


Scheme 2. (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 100%; (b) DIBALH, CH_2Cl_2, −78 °C, 99%; (c) $NaBH_4$, MeOH/THF, 0 °C, 100%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) PhSeSePh, $NaBH_4$, EtOH, rt, 96% (two steps); (f) *m*CPBA, CH_2Cl_2, 0 °C; then Et_3N, 35 °C, 85%.

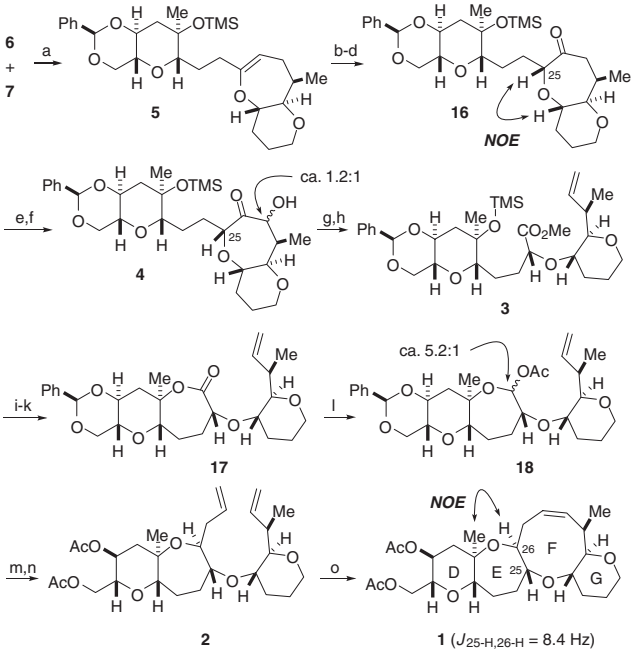
delivered **6** in good overall yield.

The synthesis of enol phosphate **7** started with a three-step conversion of the known alcohol **10**[10] into methyl ketone **11** (Scheme 3). The Wittig methylenation of **11** gave olefin **12**, which was hydroborated with dicyclohexylborane to afford alcohol **13** as a single stereoisomer.[11] After conversion to diol **14**, oxidative lactonization using TEMPO/PhI$(OAc)_2$[12] furnished seven-membered lactone **15**. Treatment of **15** with KHMDS/$(PhO)_2P(O)Cl$ delivered enol phosphate **7**.

With the requisite fragments in hand, we then proceeded to construct the EF-ring domain (Scheme 4). Hydroboration of **6** using 9-BBN-H generated an alkylborane, which without isolation was coupled with **7** under the influence of $Pd(PPh_3)_4$ catalyst and aqueous Cs_2CO_3 (THF/DMF, 50 °C), leading to enol ether **5** in 96% yield. Hydroboration of **5** using $BH_3 \cdot SMe_2$ in THF at room temperature gave an approximately 2.5:1 mixture of inseparable diastereomeric alcohols.[13] Subsequent oxidation provided a 2.5:1 mixture of ketone **16** and its C25-epimer. Exposure of the mixture of diastereomers to DBU in toluene at 100 °C led to epimerization at C25, resulting in enrichment of the desired **16** in a 14:1 ratio. Enolization of **16** in the presence of



Scheme 3. (a) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C; (b) MeMgBr, THF, 0 °C, 88% (dr = 4:1, two steps); (c) PCC, 4 Å MS, CH_2Cl_2, rt, 87%; (d) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, −78 to 0 °C, 94%; (e) Cy_2BH, THF, rt; then aq NaOH, H_2O_2, rt; (f) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C; (g) $Ph_3P{=}CHCO_2Et$, THF, rt, 87% (three steps); (h) H_2, Pd/C, EtOAc, rt; (i) $LiAlH_4$, THF, 0 °C; (j) CSA, MeOH, rt, 100% (three steps); (k) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 90%; (l) KHMDS, $(PhO)_2P(O)Cl$, HMPA, THF, −78 °C.



Scheme 4. (a) **6**, 9-BBN-H, THF, rt; then aq Cs_2CO_3, **7**, $Pd(PPh_3)_4$, DMF, 50 °C, 96%; (b) BH_3·SMe_2, THF, rt; then aq NaOH, H_2O_2, rt, 100% (dr = 2.5:1); (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 99%; (d) DBU, toluene, 100 °C, 100% (dr = 14:1); (e) LiHMDS, TMSCl, Et_3N, THF, −78 to 0 °C; (f) OsO_4, NMO, THF/H_2O, rt, 86% (two steps); (g) $Pb(OAc)_4$, $NaHCO_3$, MeOH/benzene, rt; (h) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, 0 °C, 84% (two steps); (i) TBAF, AcOH, THF, rt, 100%; (j) LiOH, THF/MeOH/H_2O, rt, 88%; (k) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, rt; then DMAP, toluene, 100 °C, 90%; (l) DIBALH, CH_2Cl_2, −78 °C; then Ac_2O, pyridine, DMAP, −78 to 0 °C, 97%; (m) allylSiMe$_3$, BF_3·OEt_2, 4 Å MS, CH_3CN/CH_2Cl_2, −40 °C to rt, 78%; (n) Ac_2O, DMAP, THF, rt, 72%; (o) Grubbs' 2nd-generation catalyst, CH_2Cl_2, 40 °C, 100%.

TMSCl/Et_3N gave an enol silane, which was oxidized with OsO_4/NMO to afford α-hydroxy ketone **4** as a 1.2:1 mixture of diastereomers. Treatment of **4** with $Pb(OAc)_4$ in MeOH/benzene followed by the Wittig methylenation furnished ester **3**. Deprotection of the silyl group, saponification of the methyl ester, and subsequent lactonization under Yamaguchi conditions[14] gave lactone **17**. Reduction of **17** with DIBALH followed by in situ acylation[15] delivered acetate **18** as a 5.2:1 mixture of diastereomers. Stereoselective allylation[2a] of **18** was effected by its treatment with allyltrimethylsilane and BF_3·OEt_2, leading to diene **2** after acetylation. Finally, exposure of **2** to the Grubbs second-generation catalyst (CH_2Cl_2, 40 °C)[16] furnished the tetracyclic ether **1**, which corresponds to the DEFG-ring skeleton of GAs. The stereochemistries at C25 and C26 were unequivocally determined by an NOE experiment and $^3J_{H,H}$ value as shown.

In conclusion, we have devised a new strategy for the stereocontrolled synthesis of the DEFG-ring skeleton of GAs based on the Suzuki–Miyaura coupling as the fragment assembly process. The C25 stereogenic center was successfully elaborated by hydroboration of **5** and subsequent oxidation/epimerization sequence. Further studies toward the completion of the total synthesis of GAs are in progress.[17]

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