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# Stereoselective Synthesis of *trans*-Fused 7,6,6,7-Membered Tetracyclic Ether, Corresponding to the EFGH-Ring of Gambierol and the BCDE-Ring of Gambieric Acids

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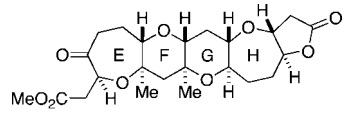
## ABSTRACT




**Stereoselective synthesis of a *trans*-fused 7,6,6,7-membered tetracyclic ether, corresponding to the EFGH-ring of gambierol and the BCDE-ring of gambieric acids, was efficiently accomplished via a two-directional approach. The key reactions were $SmI_2$-induced double cyclization for construction of the F- and H-rings and $SmI_2$-induced cyclization followed by ring expansion for construction of the E-ring.**

Marine polycyclic ethers, exemplified by brevetoxins, have attracted much attention among organic chemists as a result of their complex structures and potent bioactivities.[1,2] Gambierol (**1**)[3] was isolated by Yasumoto et al. from cultured cells of the ciguatera-causative dinoflagellate *Gambierdiscus toxicus* (Figure 1). Structurally, it consists of a *trans*-fused 6,6,6,6,7,6,6,7-membered octacyclic ether core (ABCDEFGH-ring) containing 18 chiral centers and a triene side chain, including a conjugated (*Z*,*Z*)-diene system. Gambierol (**1**) exhibits potent toxicity in mice ($LD_{50}$ = 50 $\mu$g/kg), and its symptoms resemble those caused by ciguatoxins, which are commonly associated with seafood poisoning. Yasumoto et al. also isolated gambieric acids A−D (**2a**−**d**)[4] as related natural products, which contain a tetrahydrofuran (A-ring) and *trans*-fused 7,6,6,7,9,6,6,6,6-membered nonacyclic ether (BCDEFGHIJ-ring) core. The BCDE-ring system of **2** is closely similar to the EFGH-ring system of **1**. Recently, Fuwa, Sasaki et al. synthesized the A/B-ring fragment of the originally assigned structure of gambieric acid B and its possible diastereomers.[5] Detailed comparison of their NMR data with those of natural gambieric acid B culminated in a stereochemistry reassignment of the relative structure of the A/B-ring fragment and the absolute configuration of gambieric acids (**2**) as shown in Figure 1.

Extensive synthetic studies have been directed toward **1** and **2**,[6,7] and total syntheses of gambierol (**1**) have been independently accomplished based on a convergent strategy by the Sasaki,[8] Kadota and Yamamoto,[9] and Rainier[10] groups.

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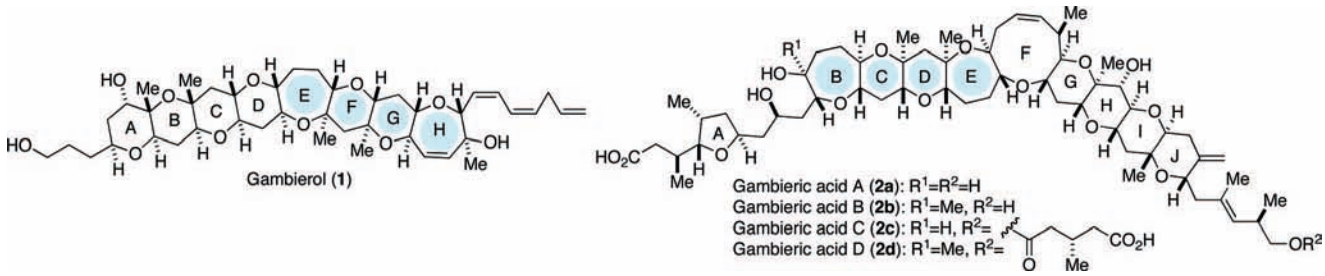


**Figure 1.** Structures of gambierol (**1**) and gambieric acids (**2**).

We now report a stereoselective synthesis of the *trans*-fused 7,6,6,7-membered tetracyclic ether **20**, corresponding to the EFGH-ring of gambierol (**1**) and the BCDE-ring of gambieric acids (**2**). Our synthesis features an efficient two-directional synthetic strategy by utilizing our developed $SmI_2$-induced reductive cyclization for the construction of *trans*-fused polycyclic ethers.[11]

The synthesis of the functionalized G-ring **10** started with the known diol **3**,[6g] prepared from commercially available 2-deoxy-D-ribose (Scheme 1).[12] Hydrogenolysis of the benzylidene acetal **3** on $Pd(OH)_2/C$ quantitatively afforded the tetraol **4**, and we then examined whether double triflation and double TBS protection could be conducted in one pot to obtain the bis(triflate) **5**, since triflation under usual conditions[13] using several equivalents of 2,6-lutidine as a base resulted in low yield. After several attempts, the desired double triflation of the tetraol **4** with $Tf_2O$ was realized in a 1:1 mixture of 2,6-lutidine and $CH_2Cl_2$ as the reaction solvent at −78 °C, and subsequent addition of TBSOTf in one pot afforded the bis(triflate) **5**. Regioselective mono-allylation of the bis(triflate) **5** was accomplished by utilizing the difference in reactivity between the two triflates. Upon treatment of **5** with allylmagnesium chloride in the presence of CuI in $Et_2O$ at −50 °C,[14] regioselective mono-allylation took place at the less-hindered right side to give the adduct **6**, which was then treated with NaCN in DMSO at 80 °C to give the nitrile **7** in 95% overall yield from **3**. Reduction of **7** with DIBALH and subsequent treatment with MeMgBr gave the alcohol **8** in 94% yield (two steps). After TPAP−NMO oxidation[15] of **8** (85%), ozonolysis of the resulting ketone **9** afforded the keto-aldehyde, which upon treatment with 6 equiv of 1,3-propanedithiol and 6 equiv of $BF_3{\cdot}Et_2O$ at 0 °C underwent double thioacetalization with simultaneous desilylation to give the desired bis(thioacetal) **10** in 95% yield (two steps). The product **10** has the required similar functional groups at the left and right sides for a two-directional synthetic strategy.

We next investigated the simultaneous construction of the F- and H-rings by double cyclization using $SmI_2$-induced reductive cyclization (Scheme 2).[11] The reaction of the diol **10** with 5 equiv of methyl propiolate in the presence of 8 equiv of *N*-methylmorpholine (NMM) resulted in double hetero-Michael addition to give the bis(*β*-alkoxyacrylate) **11** in 87% yield. Removal of two thioacetal groups was achieved with Panek's procedure using Dess−Martin periodinane[16] to give the keto-aldehyde **12** quantitatively. Upon treatment of **12** with 5 equiv of $SmI_2$ in the presence of 5 equiv of

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(12) The synthetic routes in Schemes 13 were discribed for the synthesis of the EFGH-ring of gambierol (**1**), which is corresponding to the synthesis of the BCDE-ring of gambieric acids (**2**).

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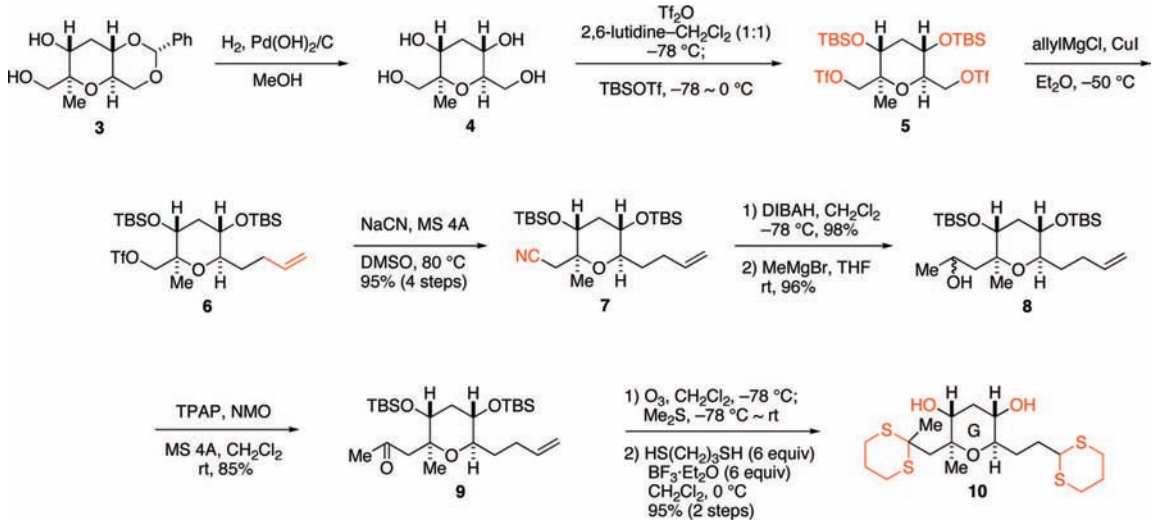
**Scheme 1**




MeOH in THF, the desired double cyclization smoothly took place at room temperature, accompanied by formation of $\gamma$-lactone, to give the tricyclic ether **13**, corresponding to the FGH-ring of **1**, in 90% yield with complete stereoselection. Thus, the tetrahydropyran F-ring having sterically hindered 1,3-diaxial dimethyl groups and the oxepane H-ring were constructed in one step. The stereostructure of **13** was confirmed by means of NMR analyses ($^1$H and $^{13}$C NMR, NOE, and HMBC).

Finally, the oxepane ring, corresponding to the E-ring, was constructed by ring expansion to oxepane subsequent to $SmI_2$-induced cyclization to tetrahydropyran (Scheme 3).[17] After TMS protection of the alcohol **13** (100%), reduction of **14** with DIBALH afforded the aldehyde-lactol, which was oxidized with TPAP−NMO oxidation to give the aldehyde-lactone **15**. Subsequent treatment of **15** with 1,3-propanedithiol and $BF_3$•$Et_2O$ provided the thioacetal **16** in 77% yield (three steps from **14**). The hetero−Michael addition of **16** and (*E*)-MeOCH═CHCO$_2$Me with PPTS in refluxing toluene[18] and subsequent removal of the thioacetal with MeI[19] provided the aldehyde **17**. Treatment of **17** with $SmI_2$ in the presence of MeOH in THF effected reductive cyclization to give 2,6-*syn*-2,3-*trans*-tetrahydropyran **18** with complete stereoselection (77% yield from **16**). The desired oxepane E-ring was then constructed by ring expansion using $TMSCHN_2$.[20,21] After TPAP−NMO oxidation of **18** (87%), the resulting ketone **19** was treated with $TMSCHN_2$ in the presence of $BF_3$•$Et_2O$ in $CH_2Cl_2$ and then with PPTS in MeOH−$CH_2Cl_2$ to give the ring-expanded product **20**, corresponding to the EFGH-ring of **1** and also the BCDE-ring of **2**, in 68% yield (two steps).[22] The stereostructure of **20** was unequivocally confirmed by means of NMR analyses ($^1$H and $^{13}$C NMR, NOE, HMBC) (Figure 2).

**Scheme 2**


(17) From our previous study,[11d] direct formation of the oxepane E-ring having a 2-methyl group by $SmI_2$-induced cyclization was anticipated to give the undesired 2,7-*anti*-oxepane. Thus, we took the present route via $SmI_2$-induced cyclization to 2,6-*syn*-tetrahydropyran followed by ring expansion to the 2,7-*syn*-oxepane E-ring.

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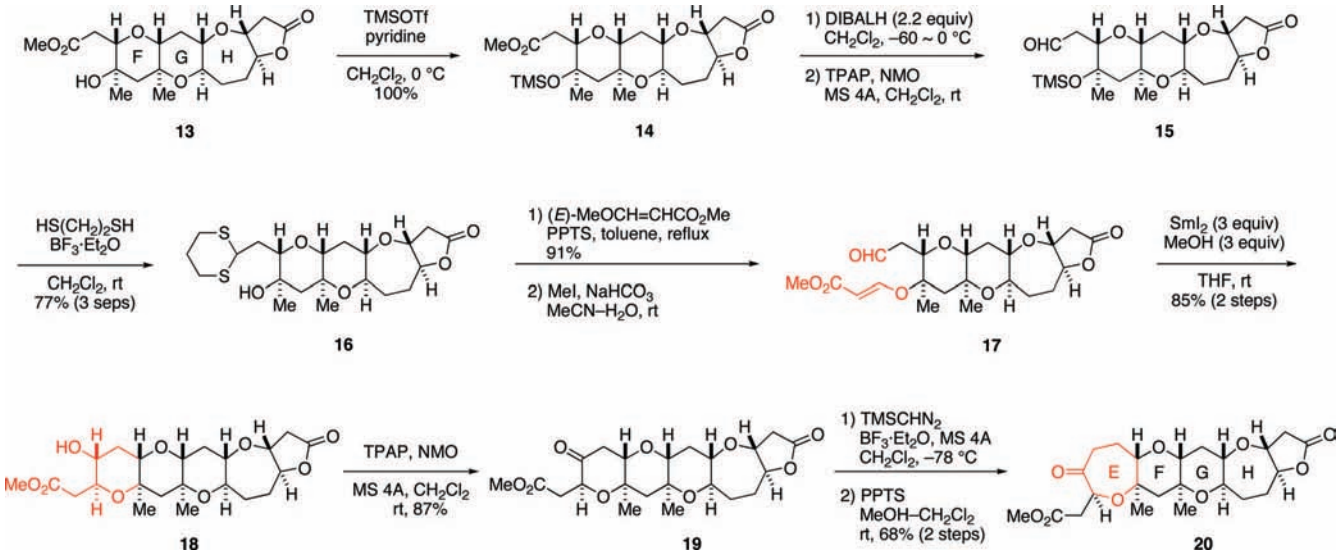
(22) The real H-ring system of gambierol (**1**), i.e., 3-hydroxy-3-methyl-4-oxepene, could be constructed from the oxepane H-ring via Itoh−Saegusa olefination followed by insertion of Me group.[8−10]

**Scheme 3**




In summary, we have synthesized the *trans*-fused 7,6,6,7-membered tetracyclic ether **20**, corresponding the EFGH-ring of gambierol (**1**) and the BCDE-ring of gambieric acids (**2**), in 22 steps with 20% overall yield from **3**. This efficient and stereoselective synthesis features a two-directional strategy, utilizing double cyclization with $SmI_2$ and $SmI_2$-induced cyclization/ring expansion as key steps.

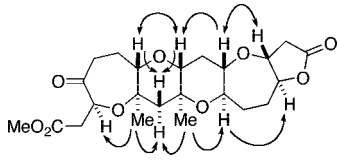


**Figure 2.** Obserbed NOEs of **20**.

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**Supporting Information Available:** Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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