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Total Synthesis of Gambierol and Its Derivatives, and Their Biological Activities

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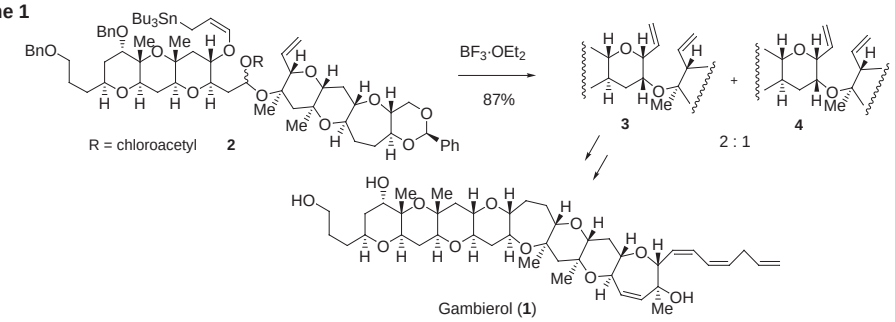
Gambierol (**1**), a marine polycyclic ether, was isolated as a toxic constituent from cultured cell of the ciguatera causative dinoflagellate, *Gambierdiscus toxicus*. The compound shows toxicity against mice (LD_{50} 50 μg/kg), and the symptoms resemble those caused by ciguatoxins inferring the possibility that it is also implicated in ciguatera poisoning. In this paper, the convergent total synthesis of gambierol (**1**) is described.[1]

Treatment of the α-chloroacetoxy ether **2** with $BF_3{\cdot}OEt_2$ gave the 2:1 mixture of the desired diene **3** and its diastereomer **4** in 87% yield (Scheme 1). Ring-closing metathesis of **3** followed by several transformations afforded gambierol (**1**). The mouse lethality of the synthetic gambierol was equal to that of the natural product. Furethermore, a variety of analogues listed in Figure 1 were synthesized to test the biological activity. However, surprisingly, all of the sturactural analogues showed no toxicity against mouse at higher concentration (5-14 mg/kg).

Scheme 1



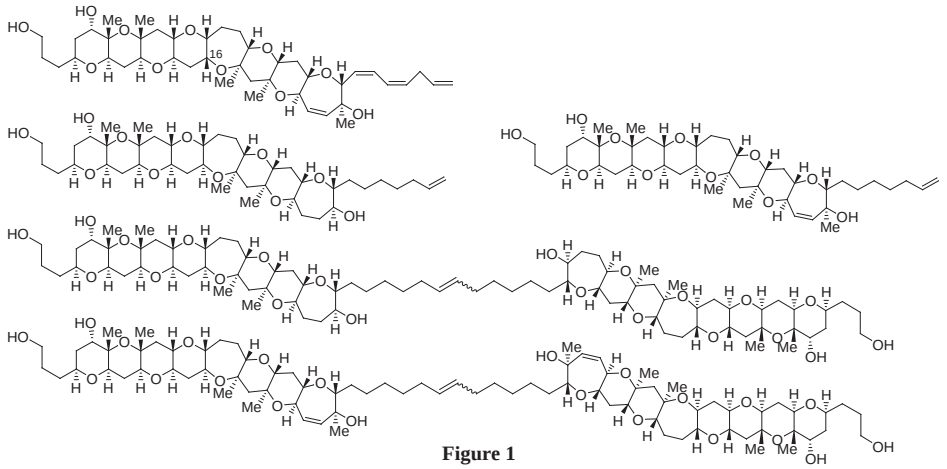


Figure 1

Reference:

1. Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893-11899.