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The absolute configuration of gambierol, a toxic marine polyether from the dinoflagellate, *Gambierdiscus toxicus*

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Abstract

The axial C6-OH group in gambierol isolated from the dinoflagellate, *Gambierdiscus toxicus*, was inverted to equatorial disposition and esterified with (*S*)- and (*R*)-MTPA. NMR analysis of these esters established *S* configuration at C6, thus allowing determination of the absolute configuration of the whole molecule.

Keywords: polyether; stereochemistry; NMR

Marine polyether compounds have fascinated many scientists by their unique and complex structures and specific biological activities, as exemplified by the brevetoxins, the ciguatoxins, and maitotoxin [1]. Although elucidation of the absolute stereochemistry of these compounds is essential for studying their mode of action, biosynthesis, and chemical synthesis, difficulties existed due to their noncrystalline nature and extremely limited availability. Recently, we successfully determined the stereostructures of ciguatoxin and its analog, yessotoxin, and pectenotoxin-6 by means of chemical derivatization, CD spectrometry, and chiral anisotropic reagents [2-4]. In this paper we report another successful determination of the absolute configuration of a marine polyether toxin, gambierol, by inversion of the C6-OH group and application of the chiral anisotropic reagent MTPA (α-methoxy-α-trifluoromethylphenylacetic acid).

Gambierol (1) was isolated from the ciguatera causative dinoflagellate, *Gambierdiscus toxicus*, and showed toxicity against mice [5]. The mice symptoms resemble those shown by ciguatoxins, implying the possibility that gambierol is also implicated in ciguatera. Therefore, determination of the absolute configuration of gambierol is important for

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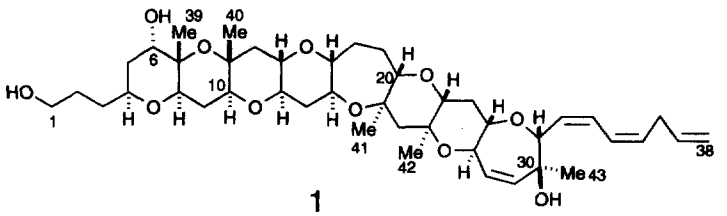
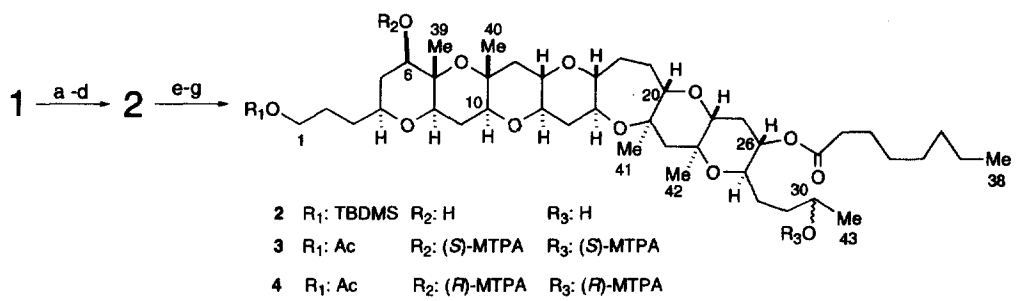
ciguatera studies and for supplying the toxin by chemical synthesis.



1

Attempted esterification at the C6 hydroxy group of **1** with anisotropic reagents, (*S*)- and (*R*)-MTPA [6], was unsuccessful because of the axial orientation of the hydroxy group. Therefore, to apply the MTPA reagents, we inverted the axial C6 hydroxy group to an equatorial orientation. Four double bonds in **1** (1 mg) were reduced by PtO_2. The C1 hydroxy group of octahydrogambierol was protected with TBDMS and the derivative was oxidized with PDC. The oxidation product was immediately reduced with $NaBH_4$ yielding an alcohol **2**. Through these stages unexpected reactions occurred: the C30-C31 bond was oxidatively cleaved, generating an octanoate ester at C26 and a hydroxy group at C30 during the following reduction. The orientation of the C6 hydroxy group was confirmed to be equatorial by the proton coupling constants of 10 and 3 Hz of H6. The resulting product **2** was divided into two portions (300 μg) and each portion was treated with (*R*)- or (*S*)-MTPA chloride and TEA in pyridine for 3 hr at room temperature. The reaction mixture was partitioned between $CHCl_3$ and H_2O and the organic solvent was removed. Each residue was purified by HPLC to give pure (*S*)- and (*R*)-MTPA esters, respectively. Finally, to avoid overlaps of NMR signals, the protecting group of the C1 hydroxy group was changed to acetates, **3** and **4**.

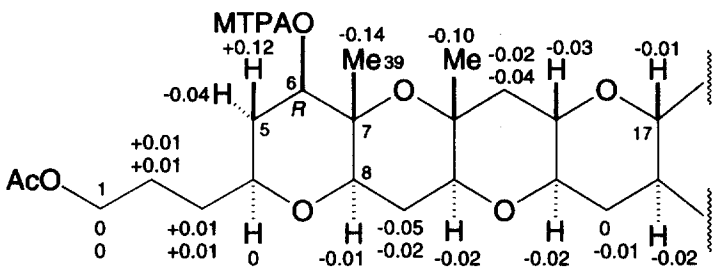


2 R_1: TBDMS R_2: H R_3: H
3 R_1: Ac R_2: (*S*)-MTPA R_3: (*S*)-MTPA
4 R_1: Ac R_2: (*R*)-MTPA R_3: (*R*)-MTPA

Reagents and conditions; a. PtO_2, H_2, EtOH; b. TBDMSCl, TEA, DMF; c. PDC, Pyr-TFA, CH_2Cl_2, 40 °C; d. $NaBH_4$, MeOH; 2 was divided into two portions e. (*R*)- or (*S*)-MTPACl, TEA, Pyr; f. AcOH/MeOH/H_2O, 40 °C; g. Ac_2O, Pyr.

The ^1H NMR spectra of **3** and **4** were measured with a 600 MHz instrument in C_5D_5N, $CDCl_3$ and CD_3OD/CD_2Cl_2 (10/85) at 20 °C. Two-dimensional NMR spectra were measured at 2 k x 256 points matrix and eight times zerofilling of the F1 axis for COSY and two times zerofilling of the F1 axis for TOCSY. By analyzing the COSY and TOCSY spectra of **3** and **4**, $\Delta\delta$ (δ_S-δ_R) values of the protons in CD_3OD/CD_2Cl_2 were obtained: they are indicated in partial structure **5**. Except for the equatorial proton at C5, the signs of $\Delta\delta$ values were clearly distributed symmetrically around C6. In the three solvents used, the signs of $\Delta\delta$ values for protons from H2 to H5-axial were positive, while those for protons from Me39 to H17 were negative. The other MTPA ester at C30 was distant from C6 and, therefore, exerted no influence on the signs of $\Delta\delta$ values around C6. We have no explanation for the negative sign of the $\Delta\delta$ value for the C5 equatorial proton. Nevertheless, the distribution of the signs of other protons well reflected the anisotropic effects of the MTPA ester at C6.

From these results, the absolute configuration at C6 in **1** was determined to be *S*. As the relative stereostructures of other asymmetric centers had been established, the present finding led to the absolute configuration of gambierol as shown in **1**.



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Many synthetic studies of marine polyether compounds have reached an advanced stage [7-9]; especially the total synthesis of brevetoxins B and A has been accomplished [10,11]. The stereochemical information obtained in this study should greatly contribute to synthetic efforts toward this intriguing molecule [12], eventually allowing toxicological and pharmacological studies of gambierol.

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