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Synthesis of the ABCD Ring of Gambierol†

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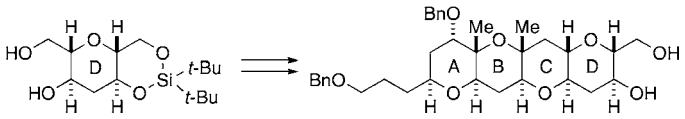
ABSTRACT



A fully functionalized ABCD ring moiety of gambierol, a marine polycyclic ether toxin, was synthesized by the use of the oxiranyl anion strategy and reductive cycloetherification of a *β*,*δ*-dihydroxy ketone.

Gambierol (**1**) is a marine polycyclic ether isolated as a neurotoxin from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*.[1] The structure consists of a trans-fused octacyclic polyether containing three hydroxy groups and a partially skipped triene side chain. The toxin exhibits potent toxicity against mice at 50 μg/kg (LD_{50}), and the symptoms it causes in mice resemble those shown for ciguatoxins.[2] The characteristic molecular architecture and potent biological activities make gambierol a challenging synthetic target,[3] and in fact, three total syntheses have been accomplished.[4]

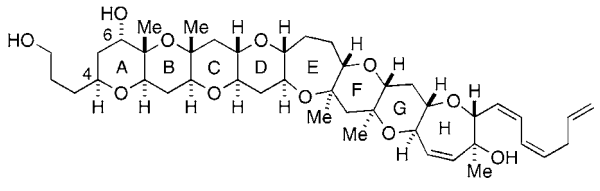


Figure 1. Structure of gambierol (**1**).

We have previously reported a useful synthetic approach to trans-fused polycyclic ether ring systems.[5] The strategy involves the alkylation of the oxiranyl anion generated from an α,*β*-epoxy sulfone followed by 6-*endo* cyclization to form a 3-keto tetrahydropyran ring. The efficiency and flexibility of this approach stimulated us to synthesize marine polycyclic ethers. We now report the synthesis of the ABCD ring system of **1**. Key features of our synthesis are the construction of the carbon backbone of the B and C rings from a single building block and the efficient formation of the A ring by the hydroxy ketone cyclization.

† This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka.

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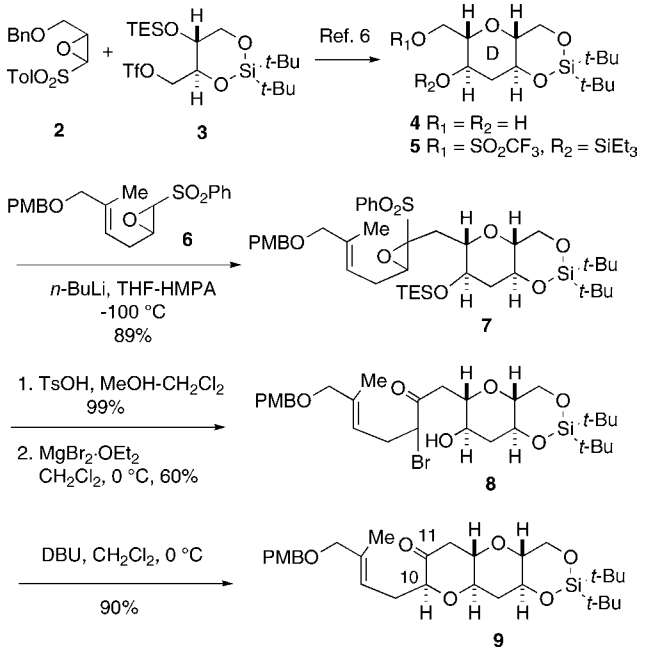
Our studies began with the optically active D ring diol **4**, which was prepared from epoxy sulfone **2** and triflate **3** in six steps (Scheme 1).[6] One-pot triflation and triethylsilylation[5b]

Scheme 1

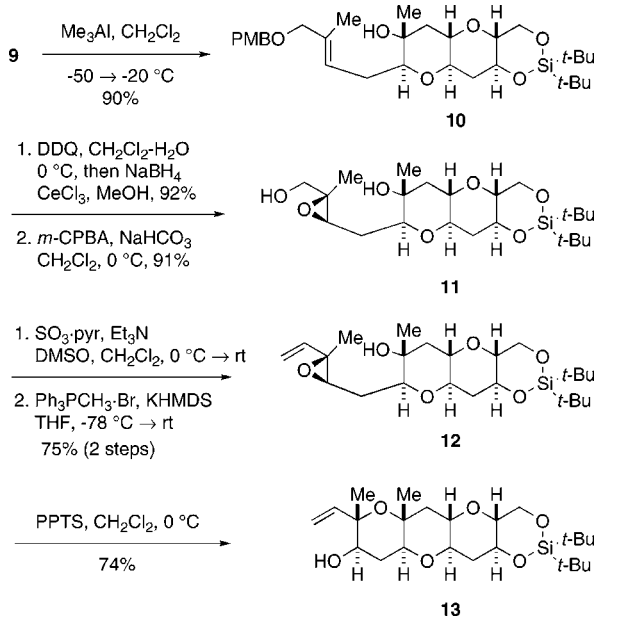


of diol **4** gave triflate **5** in 94% yield. The triflate was coupled with the oxiranyl anion generated from the racemic *trans*-α,*β*-epoxy sulfone **6** to afford a mixture of epoxy sulfones **7** composed of two diastereoisomers in 89% yield. Removal of the triethylsilyl group followed by the reaction with magnesium bromide gave a 1:1 mixture of diastereomeric bromo ketones **8**. Subjecting the mixture to cyclization with DBU yielded tricyclic ketone **9** predominantly as one diastereoisomer (dr 94:6) in good yield.[7]

This cyclization has the advantage that neither the stereochemistry of bromo ketones **8**, in turn, nor that of **7** is relevant, because the initial cyclization products undergo facile base-catalyzed equilibration to give the thermodynamically more stable isomer **9** possessing an equatorial C-10 substituent.

Stereocontrolled installation of the C-11 *β*-axial methyl group was accomplished with trimethylaluminum to provide the tertiary alcohol **10** in good selectivity (dr 94:6) (Scheme 2).[8] Removal of the PMB group of **10** with DDQ[9] gave a

Scheme 2



3:2 mixture of an allylic alcohol and the corresponding α,*β*-unsaturated aldehyde. To avoid handling of the labile aldehyde, the reaction mixture was further treated with sodium borohydride in one pot, yielding the allylic alcohol in 92% yield. The subsequent epoxidation with *m*-CPBA gave *β*-epoxy alcohol **11** in high stereoselectivity (dr 96:4),[10] which was then subjected to SO_3·pyridine oxidation and the Wittig reaction to afford vinyl epoxide **12** in 75% overall yield. The vinyl epoxide underwent a smooth cyclization in a 6-*endo* manner upon treatment with PPTS at 0 °C to afford tetracyclic vinyl alcohol **13** in 74% yield.[11]

Construction of the A ring is a challenging issue, because its α-axial hydroxy group at C-6 and *β*-equatorial three-carbon side chain at C-4 have to be installed stereoselectively. The reported methods employed asymmetric allylation of an aldehyde[3a] and reduction of a hydroxy epoxide[4b] to introduce the C-6 hydroxy group and necessitated an additional carbon−carbon bond-forming reaction and an intramolecular hetero-Michael reaction to construct the A ring. We envisioned that the hydroxy group and the side chain could be constructed by the reaction of an epoxide derived from **13** with a 2-substituted lithiodithiane (Scheme 3).

The homoallylic hydroxy-directed epoxidation[12] of **13** with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$[13]

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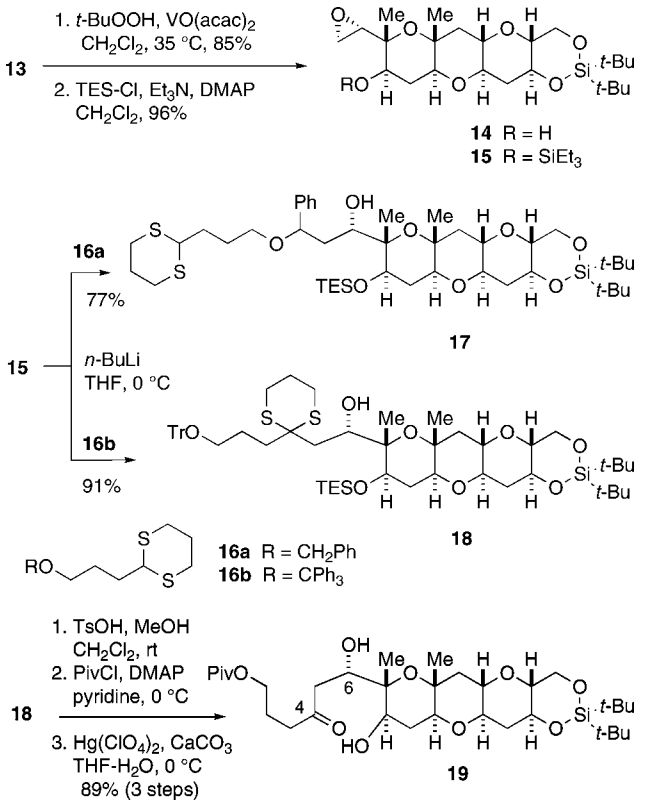
(10) Sharpless asymmetric epoxidation showed a lower diastereoselectivity (dr 81:19).

(11) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc*. **1989**, *111*, 5330−5334.

Scheme 3

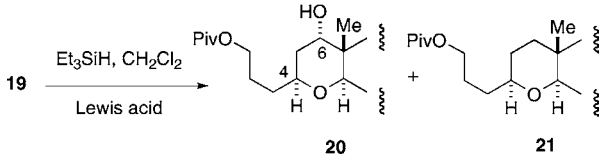


yielded the desired epoxide **14** in high selectivity (dr 93:7). The stereochemistry of the epoxide was determined by the ^{1}H NMR analysis of the acetonide derivative prepared by the reduction of the epoxide with sodium triethylborohydride followed by the reaction with 2,2-dimethoxypropane. The reaction of **15** with the lithiodithiane of benzyl ether **16a** under in situ trapping conditions gave an unexpected product **17**.[14] To avoid this undesired reaction, the tritylated dithiane **16b** was reacted with epoxide **15** to afford the desired hydroxy dithiane **18** in 9% yield. The dithioacetal **18** was transformed into β,δ-dihydroxy ketone **19** in a three-step sequence: removal of the triethylsilyl and trityl groups, pivaloylation of the primary alcohol, and hydrolysis of the dithioacetal group.

Finally, we examined the formation of the A ring by reductive cycloetherification[15] of β,δ-dihydroxy ketone **19**. It was hoped that stereochemical control would be achieved by hydride addition to the pyran oxonium ion derived from the hemiketal, which would accept a hydride from the axial direction despite the presence of the α-axial C-6 hydroxy group due to stereoelectronic reasons.[16]

The reaction of **19** with triethylsilane in the presence of BF_3·OEt_2 gave the desired product **20** only in 55% yield

Table 1. Reductive Etherification of Dihydroxy Ketone **19**

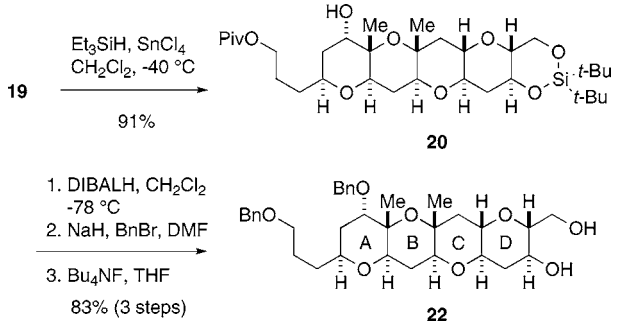


entry	Lewis acid	reaction conditions	**20** (%)[a]	**21** (%)[a]
1	BF_3·OEt_2	−40 °C, 1 h	55	21
2	$TiCl_4$	−40 °C, 1 h	28	5
3	$SnCl_4$	−78 °C, 40 min	9[b]	
4	$SnCl_4$	−40 °C, 30 min	91	

[a] Isolated yield. [b] **19** was recovered in 87% yield.

along with the deoxygenated product **21** in 21% yield (Table 1, entry 1). However, **20** was obtained in 91% yield as the sole product when $SnCl_4$ was employed at −40 °C (entry 4). It is noteworthy that dehydration of **19** to an α,β-unsaturated ketone was completely suppressed under the $SnCl_4$-promoted reduction conditions and that the axial attack of the hydride took place exclusively on the oxonium intermediate.

Scheme 4



Removal of the pivaloyl group of **20** with DIBALH, benzylation of the primary and secondary alcohols, and desilylation with TBAF gave the ABCD ring diol **22** of **1** in 83% overall yield.

In summary, we have synthesized the ABCD ring system of gambierol (**1**) in 20 synthetic transformations from diol **4**. Of note in these studies are the use of epoxy sulfone **6** as a multifunctional building block to construct the B and C rings, homoallylic hydroxy-directed stereoselective epoxidation to install the axial alcohol, and reductive

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cycloetherification of the labile β,δ-dihydroxy ketone. Further investigations directed toward the total synthesis of **1** are underway in our laboratory.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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