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A CONCISE SYNTHESIS OF THE AB-RING FRAGMENT OF (−)-GAMBIEROL

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Abstract – We describe herein a concise synthesis of the AB-ring fragment of gambierol, wherein silver(I) trifluoromethanesulfonate-catalyzed 6-*endo* cyclization of a hydroxy ynone was exploited for the formation of the A-ring.

This paper is dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

(−)-Gambierol (**1**, Figure 1) is a structurally complex marine polycyclic ether natural product that was isolated from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus* by Satake and co-workers.[1] The entire structure of **1** was elucidated by extensive 2D-NMR analysis and application of a chiral anisotropic reagent. Satake et al. have reported that gambierol exhibits potent lethal toxicity against mice with a minimal lethal dose value of 50 μg/kg (ip) and that the neurological symptoms caused in mice resemble those shown by ciguatoxins, suggesting the possible role of **1** in ciguatera seafood poisoning. Unfortunately, detailed biological studies on **1** had been precluded for almost a decade, due to the extreme natural scarcity of **1**. Motivated by the structural complexity as well as the biological aspects, we have successfully completed the first total synthesis of **1** and enabled material supply for extensive biological investigations.[2,3] Consequently, we have identified that **1** inhibits voltage-gated potassium channels (Kv channels) in mice taste cells in low nanomolar concentrations,[4] while **1** acts as a weak partial agonist of voltage-gated sodium channels in human neuroblastoma cells.[5] Snyders and co-workers have shown that **1** selectively inhibits the Kv1 and Kv3 subfamilies and that **1** binds to the previously undescribed binding site present between the S5 and S6 segments of Kv3.1 channels.[6] In addition, we have recently found that the EFGH-ring domain of **1** plays a crucial role in inhibiting voltage-gated potassium currents and that, in an *in vitro* model of Alzheimer's disease, **1** and its truncated analogues are able to lower the amyloid β (Aβ) and

hyperphosphorylated tau levels with a possible implication of Kv channel inhibition.[7] Undoubtedly, **1** represents an intriguing molecular probe for the functional analysis of Kv channels as well as for understanding downstream events of Kv channel inhibition.

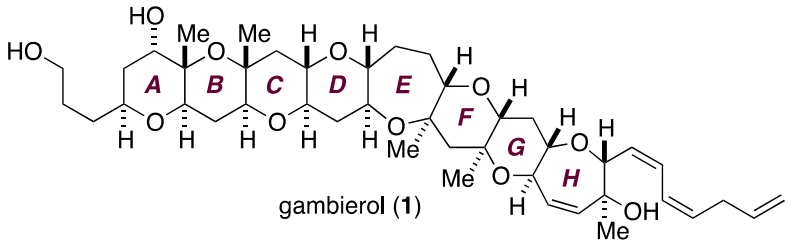
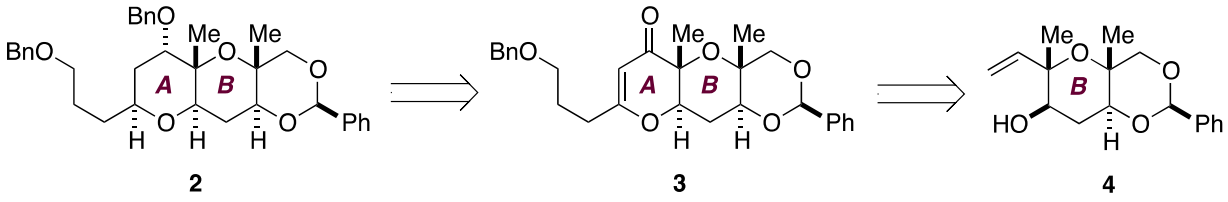


Figure 1. Structure of (−)-gambierol (**1**)

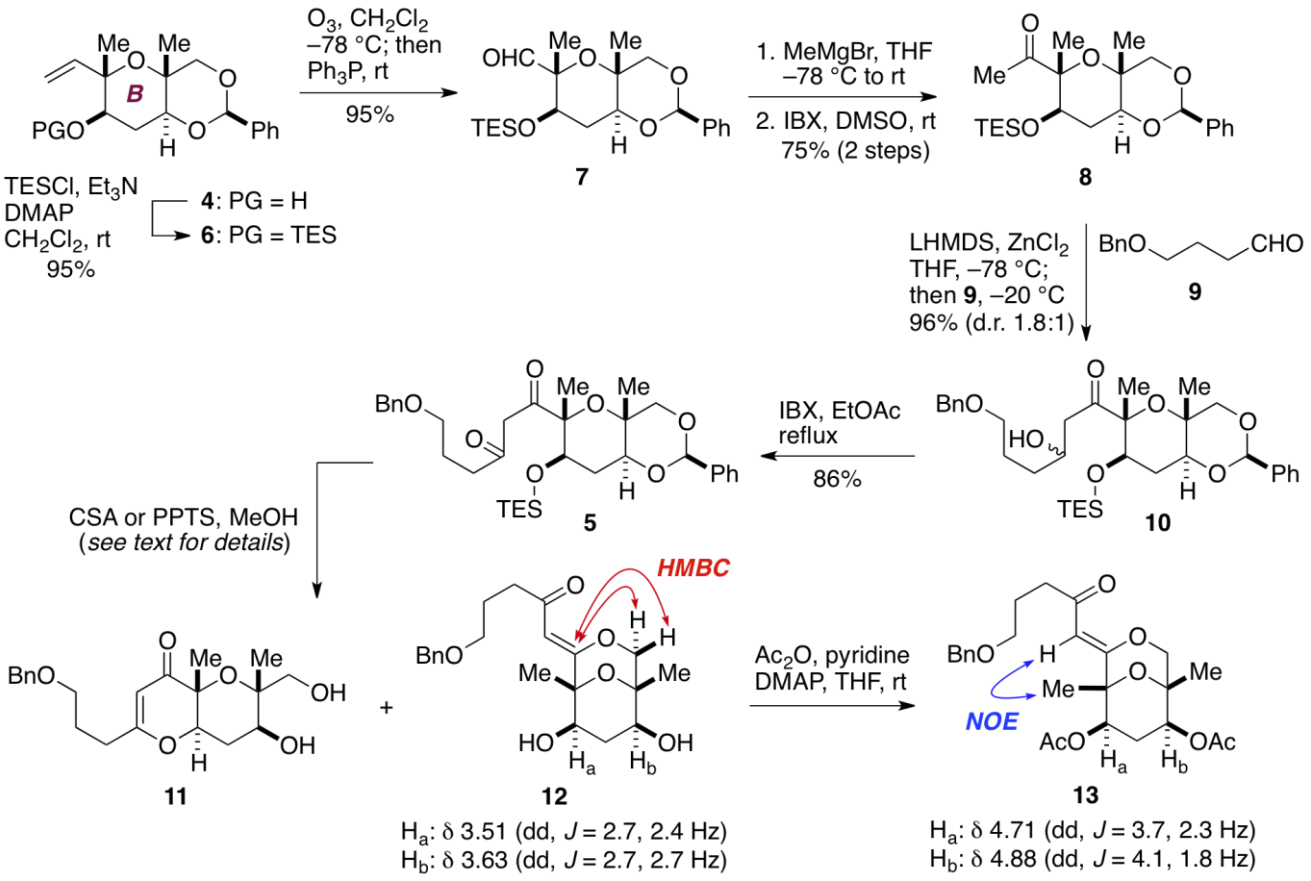
Toward an even more practical synthesis of **1**, we describe herein a concise synthesis of the AB-ring fragment of **1**. We envisioned that the AB-ring fragment **2** would be readily accessible from dihydropyrone **3**, which in turn would be obtainable from the known tetrahydropyran **4**[8] via standard chemistry (Scheme 1).



Scheme 1. Synthesis plan toward the AB-ring fragment **2**

Our initial synthetic approach toward **2** involved cyclodehydration of 1,3-diketone **5** (Scheme 2).[9] Protection of **4** with triethylsilyl chloride (TESCl) and Et_3N in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) gave TES ether **6** in 95% yield. Ozonolysis of the double bond delivered aldehyde **7** in 95% yield. Methylation with MeMgBr, followed by oxidation of the resultant alcohol with 2-iodoxybenzoic acid (IBX), provided methyl ketone **8** in 75% yield (two steps). Enolization of **8** with lithium hexamethyldisilazide (LHMDS) in the presence of $ZnCl_2$ followed by addition of 4-benzyloxybutanal (**9**) (THF, −78 to −20 °C) afforded β-hydroxy ketone **10** as a 1.8:1 mixture of diastereomers in 96% combined yield (stereochemistry not determined). Oxidation of **10** was most efficiently performed with IBX in refluxing EtOAc[10] to give 1,3-diketone **5** in 86% yield. Unexpectedly, cyclodehydration of **5** was found to be rather problematic. Treatment of **5** with (+)-10-camphorsulfonic acid (CSA) in methanol under reflux resulted in decomposition of the material, possibly due to the instability of the diketone moiety. Accordingly, **5** was reacted with CSA initially at room temperature to cleave the silyl ether and then at 60 °C to effect cyclodehydration. This modified procedure gave

dihydropyrone **11** with concomitant loss of the benzylidene acetal in 41% yield, along with a mixture of several byproducts. Careful examination of the mixture revealed that the major byproduct was bicycle **12**. Running the reaction with pyridinium *p*-toluenesulfonate (PPTS) as an acid only provided a mixture of **12** and unidentified byproducts. The structure of **12** was assigned on the basis of extensive NMR studies on **12** and its acetate **13** as shown. Upon cleavage of the benzylidene acetal, the steric repulsion existing between the 1,3-diaxial methyl groups of the tetrahydropyran would facilitate ring flipping, hemiacetal formation, and dehydration to produce **12**.

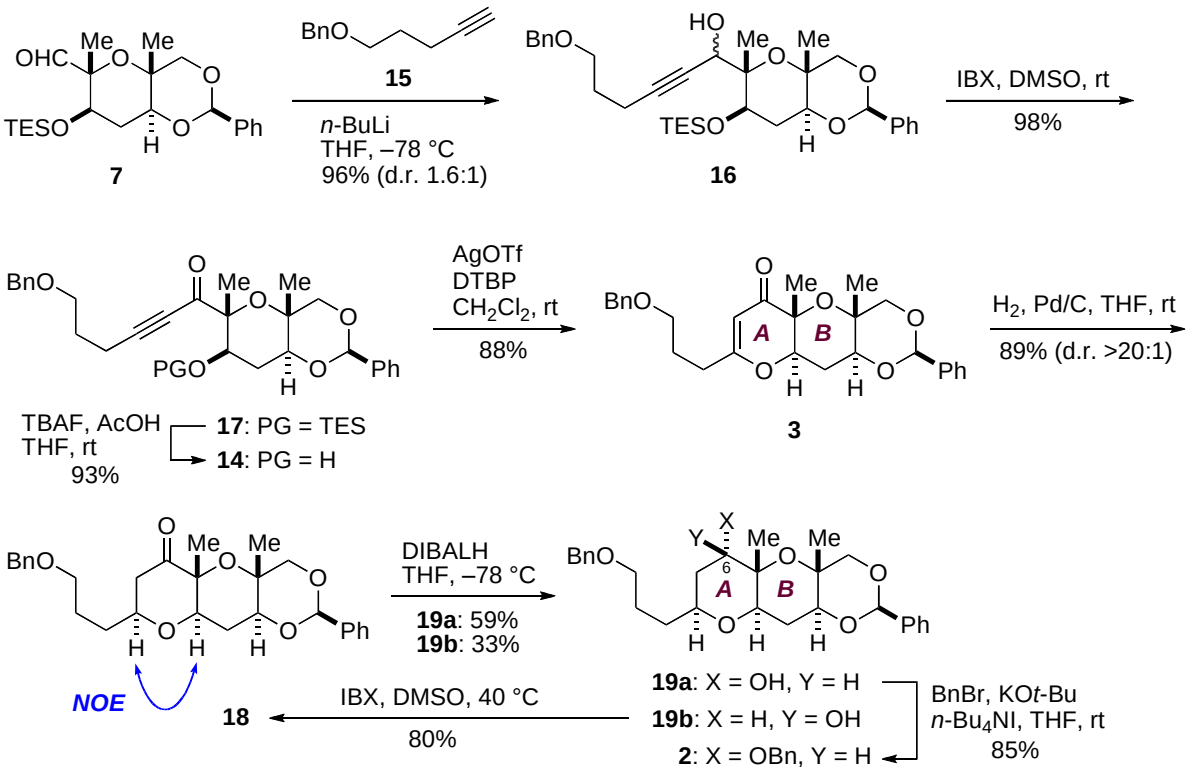


Scheme 2. Initial efforts toward the synthesis of the A-ring

The disappointing outcome of the cyclodehydration of 1,3-diketone **5** led us to investigate 6-*endo* cyclization of hydroxy ynone **14** as the revised approach toward dihydropyrone **3** (Scheme 3). We have previously shown that a variety of substituted dihydropyrones could be accessed based on silver(I) trifluoromethanesulfonate (AgOTf)-catalyzed cyclization of the corresponding hydroxy ynones.[11,12] Addition of a lithium acetylide generated from 5-benzyloxypentyne (**15**)[13] to aldehyde **7** gave propargylic alcohol **16** as a 1.6:1 mixture of diastereomers in 96% combined yield. Without separation, this material was oxidized with IBX to deliver ynone **17** in 98% yield. Removal of the TES group was effected by exposure to tetra-*n*-butylammonium fluoride (TBAF) buffered with acetic acid (93%). The resultant

hydroxy ynone **14** was cyclized smoothly upon treatment with AgOTf in the presence of 2,6-di-*tert*-butylpyridine (DTBP),[14] giving rise to dihydropyrone **3** in 88% yield.

Having established the reliable route to **3**, our focus was shifted toward elaboration of the AB-ring fragment **2** (Scheme 3). Hydrogenation of **3** proceeded in a stereoselective manner to give ketone **18** in 89% yield as a single stereoisomer. The newly generated stereogenic center was established through an NOE experiment as shown. Stereoselective reduction of **18** to establish the C6 stereogenic center turned out to be a challenging task. Even bulky reducing agents such as diisobutylaluminum hydride (DIBALH) or L-selectride® provided the desired alcohol **19a** with moderate diastereoselectivity (**19a**:**19b** = 1.4–1.8:1), while reduction with $NaBH_4$ or $LiAlH_4$ resulted in preferential formation of the undesired alcohol **19b** (**19a**:**19b** = ca. 1:6). However, we were fortunate to find that these diastereomeric alcohols were readily separable by flash chromatography on silica gel, and the undesired **19b** could be recycled by oxidation with IBX (80%).[15] Finally, benzylation of **19a** afforded bis(benzyl) ether **2** in 85% yield, successfully intercepting our previous synthesis of **1**.



Scheme 3. Synthesis of the AB-ring fragment **2** via 6-*endo* cyclization of hydroxy ynone **14**

In conclusion, we have devised a concise synthesis of the AB-ring fragment **2** of (−)-gambierol, by exploiting AgOTf-catalyzed 6-*endo* cyclization of hydroxy ynone **14**. The present synthesis allows an efficient access to **2** from the B-ring tetrahydropyran **4** in nine steps, which compares favorably with our previous synthesis (17 steps). Further studies on the chemistry and biology of (−)-gambierol and its synthetic analogues are currently underway and will be reported shortly.

ACKNOWLEDGEMENTS

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13. Alkyne **15** was prepared from aldehyde **9** in two steps ((i) CBr_4, Ph_3P, CH_2Cl_2, 0 °C; (ii) *n*-BuLi, THF, −78 °C, 96% yield for the two steps).
14. Addition of DTBP was found to be essential for obtaining **3** in excellent yield.
15. All attempts at inverting the C6 stereogenic center by means of Mitsunobu reaction were unfruitful (*p*-$NO_2C_6H_4CO_2H$, Ph_3P, diethyl azodicarboxylate, toluene or THF, reflux or *p*-$MeOC_6H_4CO_2H$, *n*-Bu_3P, *N*,*N*,*N*',*N*'-tetramethyl azodicarboxamide,[16] benzene, reflux).
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