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Concise synthesis of cyclic ethers via the palladium-catalyzed coupling of ketene acetal triflates and a zinc homoenolate. Synthesis of the DE and GH ring segments of gambierol

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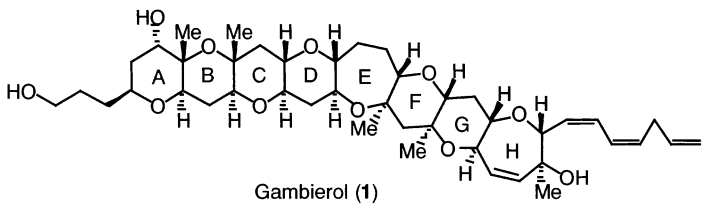
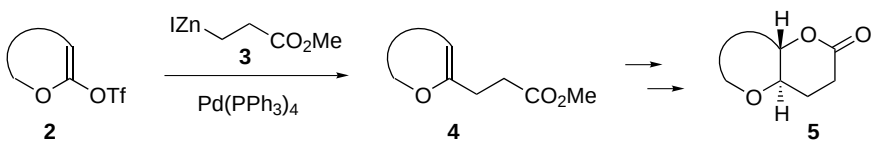
Abstract—Concise syntheses of the DE and GH ring segments of gambierol (**1**) were achieved by the palladium-catalyzed coupling of ketene acetal triflates and a zinc homoenolate, followed by the hydroboration of the resulting cyclic enol ethers and subsequent lactonization.

In recent years there has been an explosion of interest in biologically active natural products of marine origin.[1] Due to their structural novelty and toxicity, polycyclic ethers are particularly attractive targets for synthetic chemists.[2] Gambierol (**1**), a potent neurotoxin isolated from the cultured cells of *Gambierdiscus toxicus*, has 8 ether rings and 18 stereogenic centers.[3] 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.[1] We have already reported the synthesis of the E and H ring segments of **1** via the intramolecular allylstannane–aldehyde condensation.[4,5] However, the syntheses were not particularly efficient because of the relatively long synthetic schemes. For example, the E ring segment was synthesized from D-ribose in 16 steps. We now report efficient and concise syntheses of the DE and GH ring segments of **1** via the palladium-catalyzed coupling of ketene acetal triflates and a zinc homoenolate.[6]



Gambierol (**1**)

The new synthetic strategy is illustrated in Scheme 1. Since the palladium-catalyzed coupling of alkylzinc reagents and aryl halides was reported by Negishi in 1977,[7] a number of modified reactions have been developed.[8] In 1986, Tamaru reported the palladium-catalyzed coupling of alkenyl triflates, derived from ketones, and zinc homoenolates.[9] It was thought that the coupling of the *ketene acetal triflate* **2**, derived from lactones, and the zinc homoenolate **3**[10] would give the cyclic enol ether **4**, and the subsequent hydroboration



Scheme 1.

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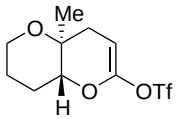
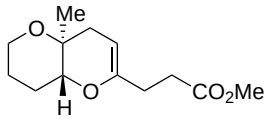
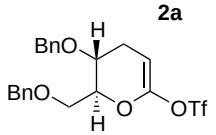
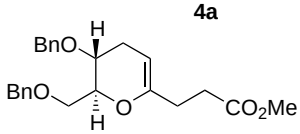
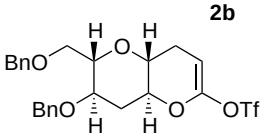
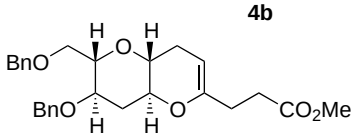
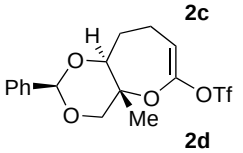
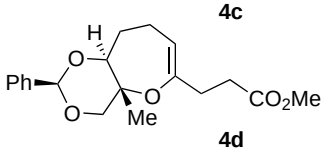
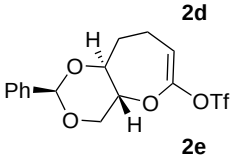
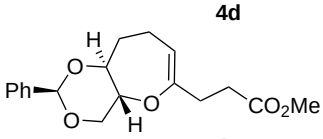
of the double bond of **4** followed by lactonization would provide the desired cyclic ether **5**.

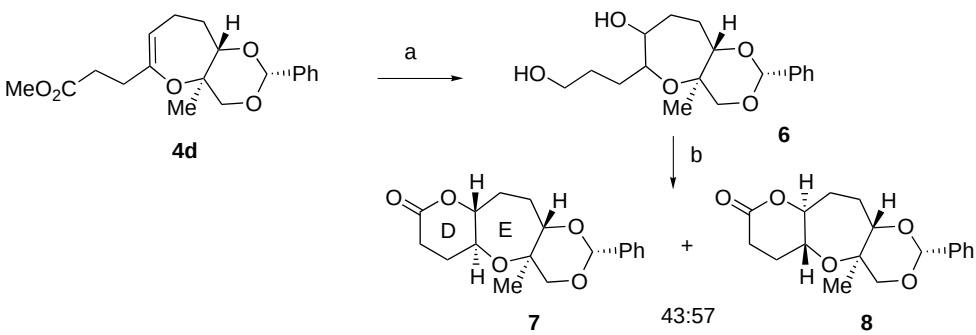
The results of the coupling of **2** and **3** are summarized in Table 1. Treatment of **2a**, prepared from the corresponding lactone by the standard procedure,[6e] with 2 equiv. of the zinc homoenolate **3** in the presence of $Pd(PPh_3)_4$ at room temperature gave the enol ether **4a** in 73% yield (entry 1). Similarly, the reaction of the six-membered ketene acetal triflates **2b** and **2c** with **3** under the same reaction conditions gave the corresponding cyclic enol ethers **4b** and **4d**, respectively, in good yields (entries 2 and 3). In order to synthesize the DE and GH rings, it was necessary to know whether the palladium-catalyzed coupling methodology is applicable to seven-membered ketene acetal triflates or not. The reaction of **2d** with **3** under the same reaction conditions afforded the desired cyclic enol ether **4d** in 82% yield (entry 4). Also, **2e** gave **4e** in 76% yield (entry 5).

The synthesis of **4a** is representative. To a suspension of Zn–Cu couple (100 mg, 1.5 mmol) in benzene (3 mL) and DMA (0.2 mL) was added methyl 3-iodopropionate (120 μL, 1.0 mmol). The mixture was refluxed for 1.5 h and then cooled to room temperature. A solution of **2a** (150 mg, 0.5 mmol) in benzene (2 mL) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) were added to the resulting mixture, successively. After being stirred for 0.5 h, the mixture was quenched with Et_3N, filtered through a silica gel pad, and concentrated. The residue

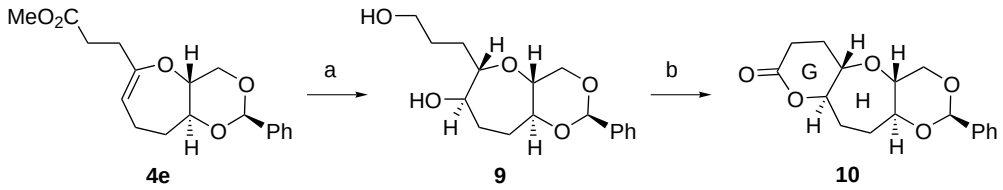
Table 1. Palladium-catalyzed coupling of ketene acetal triflates **2** and zinc homoenolate **3**[a]

entry	enol triflate[b]	product	yield[c]
1	 **2a**	 **4a**	73%
2	 **2b**	 **4b**	78%
3	 **2c**	 **4c**	74%
4	 **2d**	 **4d**	82%
5	 **2e**	 **4e**	76%

[a]Reactions were carried out with **3** (2 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol%) in benzene at room temperature.
[b]Ketene acetal triflates were prepared from the corresponding lactones by the standard procedure, and used without purification. [c]Isolated yields.



Scheme 2. (a) $BH_3{\cdot}SMe_2$, THF, 0°C to rt, then 30% H_2O_2, 3N NaOH; (b) TEMPO, NaClO, KBr, CH_2Cl_2/H_2O, 0°C, 79% from **4d**.



Scheme 3. (a) i. thexylborane, THF, 0°C–rt, then 30% H_2O_2, 3N NaOH, ii. $LiAlH_4$, ether, 0°C; (b) TEMPO, NaClO, KBr, CH_2Cl_2/H_2O, 0°C, 68% from **4e**.

was purified by silica gel chromatography using hexane/EtOAc as an eluent to give **4a** (88 mg, 73%).

We next examined the synthesis of the DE and GH ring segments of **1**. Treatment of **4d** with $BH_3{\cdot}SMe_2$ followed by oxidative work-up gave the diol **6** as a mixture of diastereomers (Scheme 2). Although the mechanism is not yet clear, the unexpected reduction of the ester group of **4d** seems to proceed via an intramolecular hydrogen transfer. TEMPO oxidation of **6** gave a 43:57 mixture of the DE ring segment **7** and its stereoisomer **8** in 79% yield from **4d**.[11] Although several attempts such as the use of bulky borane reagents were made to improve the stereoselectivity, the diastereomer ratio remained about 1:1.

Scheme 3 describes the synthesis of the GH ring segment. Hydroboration of **4e** with thexylborane gave a mixture of the diol **9** and unidentified compounds having ester and aldehyde groups. Treatment of this mixture with $LiAlH_4$ gave pure **9** as a single stereoisomer. Oxidation of **9** gave the GH ring segment **10** in 68% yield in three steps from **4e**.

In conclusion, we have developed a novel method for the concise synthesis of *trans*-fused cyclic ethers via the palladium-catalyzed coupling of ketene acetal triflates and a zinc homoenolate. We are now in a position to synthesize the DE and GH ring segments of gambierol efficiently with a shorter number of steps (11 and 10 steps from 2-deoxy-D-ribose, respectively) in comparison with previous methods.

Acknowledgements

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