Convergent Synthesis of Polycyclic Ethers via the Intramolecular Allylation of α-Acetoxy Ethers and Subsequent Ring-Closing Metathesis: Synthesis of the CDEFG Ring System of Gambierol

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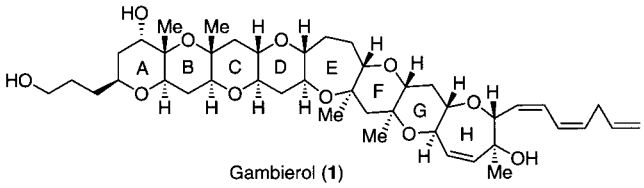
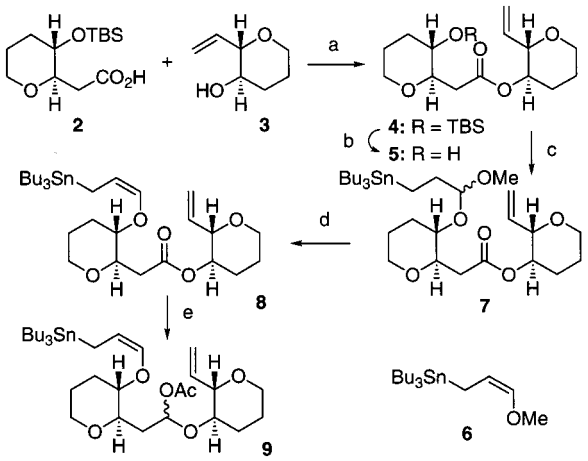
In recent years there has been an explosion of interest in biologically active natural products of marine origin.[1] Due to their structural novelty and toxicity, polycyclic ethers are particularly attractive targets for synthetic chemists.[2] Gambierol (**1**), a potent neurotoxin isolated from the cultured cells of *Gambierdiscus toxicus*, has 8 ether rings and 18 stereogenic centers.[3] As a part of the synthetic study of **1**,[4] we now report a new methodology for the convergent synthesis of polycyclic ethers via the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis.[5−7]



Gambierol (**1**)

Scheme 1[a]



[a] Reagents and conditions: (a) DCC, DMAP, CSA, CH_2Cl_2, rt, 90%; (b) TBAF, THF, rt, 100%; (c) **6**, CSA, CH_2Cl_2, rt, 95%; (d) TMSI, HMDS, CH_2Cl_2, −15 °C, 76%; (e) DIBALH, CH_2Cl_2, −78 °C, then Ac_2O, pyridine, DMAP, −78 °C to rt, 95%.

The synthesis of α-acetoxy ethers is rather straightforward and easy, and the synthesis of **9** is representative (Scheme 1). The carboxylic acid **2** and alcohol **3** were connected by DCC coupling to give the ester **4** in 90% yield. After deprotection of the silyloxy group, the alcohol **5** was converted to the allylic stannane **8** via the mixed acetal **7** in good yield.[8] The ester **8** was then subjected to the Rychnovsky protocol to give the α-acetoxy ether **9** as a mixture of diastereoisomers in 95% yield.[9]

The cyclization precursors **10**−**13** were prepared in a similar manner, and the results of the cyclization are summarized in Table 1. Treatment of **9** with 4 equiv of $BF_3{\cdot}OEt_2$ gave a 70:30 mixture of the cyclized products **14** and **15** in 79% yield (entry 1).[10] The ^{1}H NMR spectrum of **14** was identical with that of the known compound.[6d] The stereochemistry of the minor isomer **15** was confirmed by ^{1}H NMR analysis and NOE experiments. Higher stereoselectivities were observed in the formation of seven-membered rings; the reactions of **10** and **11** with $MgBr_2{\cdot}OEt_2$ afforded the corresponding cyclic ethers **16** and **18**, respectively, as major products (entries 2 and 3).[11] The reaction of the tetrabenzyl ether **12** gave **20** as a sole product in 64% yield (entry 4). In the total synthesis of **1**, one of the most difficult problems we had encountered was the introduction of *two bridgehead methyl groups* of the EFG ring. We examined several conceivable approaches to this problem, but all of the attempts resulted in failure. However, **13** could be synthesized rather easily from the corresponding tertiary alcohol, and the cyclization with $MgBr_2{\cdot}OEt_2$ gave a 71:29 mixture of **21** and **22** in 95% yield (entry 5).

We next examined the ring-closing metathesis of the products **16**, **18**, **20**, and **21** (Table 2).[7,12] Treatment of **16** with Grubbs

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(11) The use of $BF_3{\cdot}OEt_2$ gave slightly lower yields.

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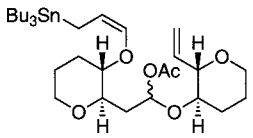
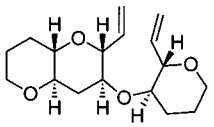
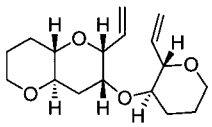
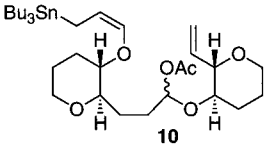
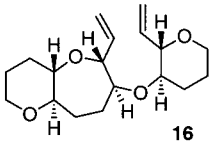
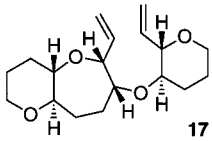
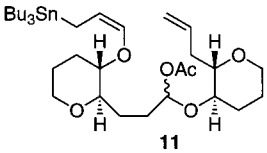
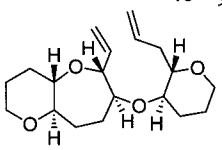
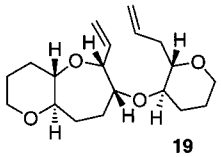
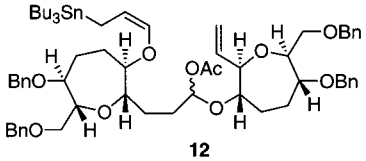
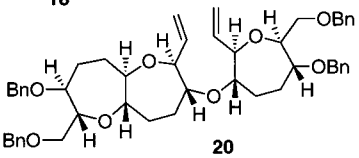
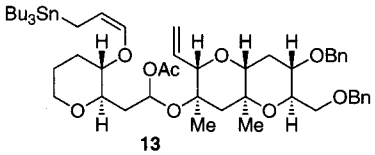
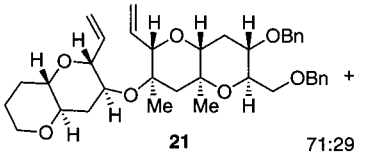
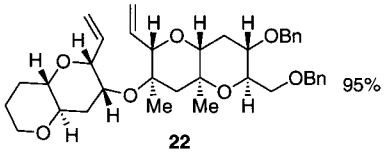
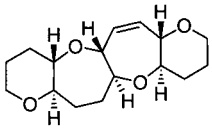
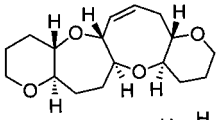
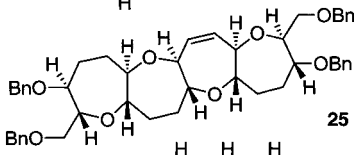
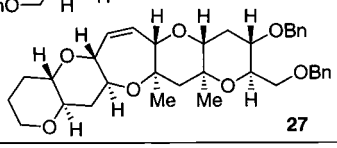
Table 1. Intramolecular Reaction of γ-Alkoxyallylstannane and α-Acetoxy Ether[a]

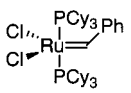
entry	substrate	products		yield[b]
1[c]	 **9**	 **14** +  **15**	70:30	79%
2	 **10**	 **16** +  **17**	>95:5	73%
3	 **11**	 **18** +  **19**	87:13	67%
4	 **12**	 **20**		64%
5	 **13**	 **21** +  **22**	71:29	95%

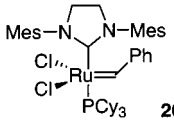
[a] Reactions were carried out with 4 equiv of $MgBr_2 \cdot OEt_2$ in the presence of molecular sieves 4 Å in CH_2Cl_2 at −20 °C. [b] Isolated yield. [c] $BF_3 \cdot OEt_2$ was used as a Lewis acid.

Table 2. Ring-Closing Metathesis of Dienes **16**, **18**, **20**, and **21**[a]

entry	substrate	product	yield[b]
1	**16**	 **23**	91%
2	**18**	 **24**	64%
3	**20**	 **25**	84%
4[c]	**21**	 **27**	84%

[a] Reactions were carried out with 20 mol % of **22** in CH_2Cl_2 at 35 °C. [b] Isolated yield. [c] Ruthenium complex **26** was used as a catalyst.

 **22**

 **26**

catalyst **22**[13] gave the tetracyclic ether **23** in 91% yield (entry 1). Similarly, the reactions of **18** and **20** proceeded smoothly to afford the corresponding polycyclic ethers **24** and **25** in 64 and 84% yields, respectively (entries 2 and 3). Although no reaction took place with **21** in the presence of **22**, the use of the more active catalyst **26** provided the desired pentacyclic ether **27**, corresponding to the CDEFG ring system of **1**, in 84% yield (entry 4).[14]

In conclusion, we have developed an efficient and flexible method for the convergent synthesis of various polycyclic ethers via the intramolecular allylation of α-*acetoxy ethers* and subsequent ring-closing metathesis. It should be noted that the use of esterification reaction, one of the most common transformations in organic synthesis, for the segment coupling makes the present methodology reliable and practical (Scheme 1). Furthermore, the new method allows a facile synthesis of the CDEFG ring system of **1**, which was difficult to prepare due to the presence of the two bridgehead methyl groups.

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Supporting Information Available: Experimental procedures and characterization data for **4**, **5**, **7**−**16**, **18**−**25**, and **27** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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