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Synthesis of the EF-Ring of Ciguatoxin 3C Based on the [2,3]-Wittig Rearrangement and Ring-Closing Olefin Metathesis

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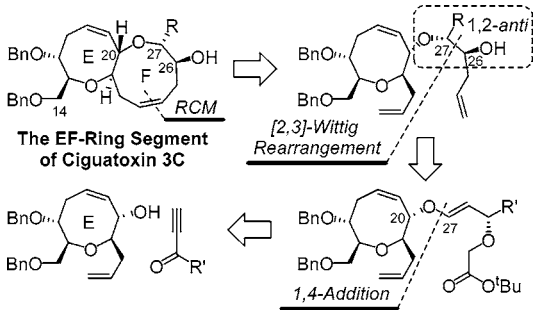
ABSTRACT



The EF-ring segment of ciguatoxin 3C, a causative toxin of ciguatera fish poisoning, was synthesized in three major steps: 1,4-addition for the C20O−C27 bond connection, chirality transferring *anti* selective [2,3]-Wittig rearrangement for the construction of the *anti*-2-hydroxyalkyl ether part, and ring-closing olefin metathesis for the F-ring formation.

Ciguatoxin 3C (**1**, Figure 1), isolated from cultured dinoflagellate *Gambierdiscus toxicus*, is a member of the ciguatera-toxin family that causes widespread seafood poisoning in circumtropical areas.[1] The potent toxicity of **1** (MLD = 1.3 μg/kg, ip, in mice)[1] is attributed to unrelenting activation of voltage-gated sodium channels by strong binding of **1** to the channel ($Ki = 0.81 \times 10^{-4}$ μM).[2] This strong binding suggests that **1** could be a potentially useful biological tool.[3] Despite the demand for significant quantities of **1** for biological research into preventing ciguatera toxicity,[4] its supply is limited due to low productivity of the toxin by *G. toxicus* (0.7 mg of **1** from 1100 L of culture).[1]

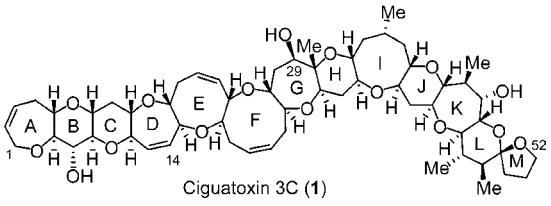


Figure 1.

Therefore, chemical synthesis is a logical approach for generating an adequate supply of **1**.

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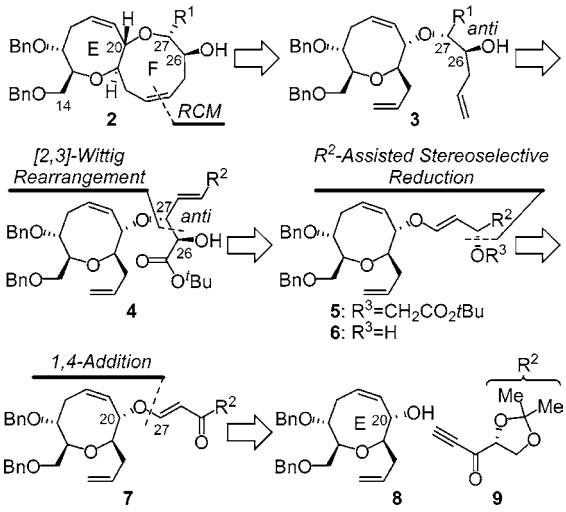
The structure of **1** consists of 12 trans-fused cyclic ethers, a spirocyclic acetal, and 30 stereocenters. This structure is extremely complex in molecular size, topology, and stereochemistry, making **1** an attractive and difficult synthetic challenge. Hence, many chemists,[5,6] including our group,[7] have long investigated the synthesis of **1** and its congeners. The Hirama group achieved the first total synthesis of **1** in 2001;[8] now the challenge is focused on increasing the efficiency of the synthesis.[9] As a part of our program toward the total synthesis of **1**, we describe here an efficient synthesis of the EF-ring segment (**2**, Scheme 1).

Our plan for the synthesis of the EF-ring segment (**2**) of **1** is shown in Scheme 1. F-ring construction from intermediate **3** by ring-closing olefin metathesis (RCM)[10,11] was scheduled at the final stage of the synthesis. To establish the *anti*-relationship of the two oxygen functional groups at C26 and C27 of **3**,[12] the [2,3]-Wittig rearrangement of (3-alkoxyallyloxy)acetate **5** to *anti*-3-alkoxy-2-hydroxyester **4** was used. This would readily lead to **3** in a chirality-transferring manner.[13] Although only a few examples of *anti*-preference in the [2,3]-Wittig rearrangement of allyloxyacetate esters have been reported,[14] we succeeded in finding conditions for providing the desired 1,2-*anti* product **4** selectively. We chose to synthesize allyl alcohol **6**, a precursor of **5**, by the 1,4-addition of **8**[15] (the E-ring segment of **1**) to an alkynone under mild conditions.[16] This was followed by the subsequent stereoselective reduction of the resulting ketone **7** with the assistance of the R^2 group as a chiral auxiliary. Here, a 2,2-dimethyl-1,3-dioxolan-4-yl group, previously reported to be efficient for stereoselective reduction of the adjacent ketone,[17] was employed as a chiral auxiliary. Therefore, the synthesis was started from alkynone **9**,[18] readily accessible from (*R*)-2,3-*O*-isopropylideneglyceraldehyde.[19]

At first, in order to establish the above-mentioned process toward an *anti*-3-alkoxy-2-hydroxy ester, acetylene ketone **9** was examined with simple alcohols (**10**) (Scheme 2). 1,4-Addition, initiated by the portionwise addition of Bu_3P (0.2−0.7 equiv) to a solution of an alcohol (**10a**−**e**) and **9** in CH_2Cl_2 at 0 °C, provided adducts **11a**−**e** with high *E*-selectivity. Although primary alcohols **10a**,**b** and simple

Scheme 1



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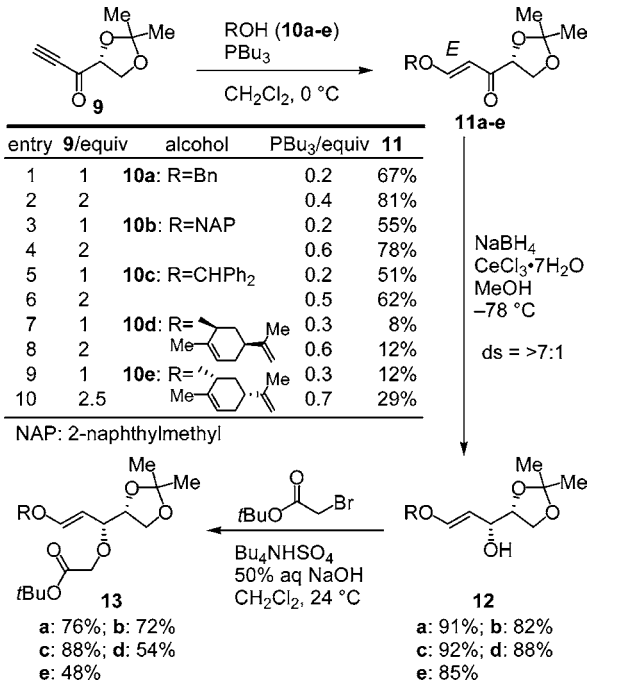
Scheme 2



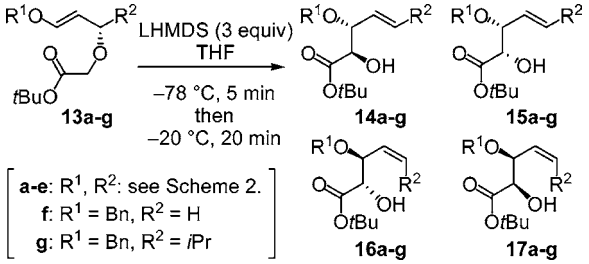
entry	9/equiv	alcohol	PBu_3/equiv	11
1	1	**10a**: R=Bn	0.2	67%
2	2		0.4	81%
3	1	**10b**: R=NAP	0.2	55%
4	2		0.6	78%
5	1	**10c**: R=$CHPh_2$	0.2	51%
6	2		0.5	62%
7	1	**10d**: R=	0.3	8%
8	2		0.6	12%
9	1	**10e**: R=	0.3	12%
10	2.5		0.7	29%

NAP: 2-naphthylmethyl

secondary alcohol **10c** showed moderate yields of **11a**−**c** (51−67%) in their reaction with an equimolar amount of **9**, the use of 2 equiv of **9** improved the yields (62−81%) (entries 1−6). The low yields in the reactions of (1*S*,5*S*)- and (1*R*,5*R*)-carveols (**10d** and **10e**) with 1 equiv of **9** (entries 7 and 9) are attributable to slow reaction rates due to steric hindrance of carveols and competition of catalyst deactivation caused by the side reaction of Bu_3P with **9**.[20] These yields were also improved significantly by the use of 2 or more equiv of **9** (entries 8 and 10). The chiral-auxiliary-assisted stereoselective reduction of **11a**−**e** was achieved by $NaBH_4$ in the presence of $CeCl_3$ to produce **12a**−**e** with relatively high selectivity (>7:1).[21] The resulting alcohols were reacted with *tert*-butyl bromoacetate under phase-transfer conditions to give **13a**−**e** in good yield.[22,23]

Representative results from the [2,3]-Wittig rearrangement of **13** are shown in Table 1. The rearrangement was typically carried out by deprotonation of **13** with 3 equiv of LHMDS[24] in THF at −78 °C followed by warming to −20 °C. The rearrangement of primary alkyl ethers **13a** and **13b** produced

Table 1.



entry	substrate	yield, %	ratio[a] **14**:**15**:**16**:**17**
1	**13a**	85	3.6:1:0:0
2	**13b**	74	3.5:1:0:0
3	**13c**	71	4:1:0:0
4	**13d**	73	6:1:0:0
5	**13e**	60	11:1:0:0
6	**13f**	81	*anti*:*syn* = 1:3
7	**13g**[b]	86	1:1.1:0:0.4

[a] Each ratio was determined by ^1H NMR. [b] Racemic **13g** was used.

14 and **15** in good yield with exclusive *E*-selectivity and reasonable *anti*-selectivity (**14a**:**15a** = 3.6:1; **14b**:**15b** = 3.5:1) (entries 1 and 2). While diphenylmethyl ether **13c** gave a similar result to that of **13a** (entry 3), (1*S*,5*S*)- and (1*R*,5*R*)-carveyl ethers **13d** and **13e** displayed excellent ratios of **14** (**14**:**15** = 6−11:1) (entries 4 and 5). These results indicated that increasing the bulkiness of the R^1 group would enhance the preference for **14**. Therefore, higher *anti*-selectivity in the [2,3]-Wittig rearrangement in the synthesis of the EF-ring of **1** was predicted if a bulky oxocene ring (E-ring) for the R^1 group of the substrate was used. Notably, R^2-modified substrates **13f** (R^2 = H) and **13g** (R^2 = *i*Pr) showed *syn*-selectivity (entry 6) and production of **14**, **15**, and **17** with low selectivity (entry 7), respectively. These results suggested that the 2,2-dimethyl-1,3-dioxolanyl group at R^2 also contributed to the preference for **14** in the [2,3]-Wittig rearrangement, even though the mechanism of this contribution is presently unclear.

Encouraged by the above results, we next synthesized the EF-ring segment (**24**) of **1** (Scheme 3). The 1,4-addition of **8** to **9** successfully provided **18**, although the reaction had to be repeated for complete consumption of **8**. The reduction of **18** with $NaBH_4/CeCl_3$ exclusively gave **19** (99% from **8**), which was reacted with *tert*-butyl bromoacetate to afford **20** (94%). The [2,3]-Wittig rearrangement of **20**, performed by treatment with LHMDS in THF at −78 °C followed by warming to 0 °C, provided **21** in high yield (86%) with almost complete stereoselectivity, in accordance with the above prediction. The ester **21** was reduced with $LiBH_4$ to an alcohol, which was converted to epoxide **22** by regioselective tosylation[25] followed by base treatment (77% from **21**). The reaction of **22** with vinyl cyano-cuprate in the presence of $Et_2O{\cdot}BF_3$ successfully produced **23** (87%).[26]

(20) The portionwise addition of 0.4 equiv of Bu_3P to **9** in the absence of an alcohol resulted in complete consumption of **9** and production of a mixture of highly polar compounds. This side reaction is serious in the case of secondary alkyl alcohols (i.e., cyclohexanol and 3-pentanol), which hardly reacted with **9**. Secondary alcohols that have at least one sp^2 carbon adjacent to a carbinol group can react with excess **9** to produce the corresponding adducts in moderate yields.

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(24) When NHMDS or KHMDS was used instead of LHMDS in preliminary experiments with **13a**, low *E*/*Z* and *anti*/*syn* selectivities were observed (NHMDS: **14a**:**15a**:**16a**:**17a** = 1.5:2.3:1:2.3; KHMDS: **14a**:**15a**:**16a**:**17a** = 5:1:0:6.5).

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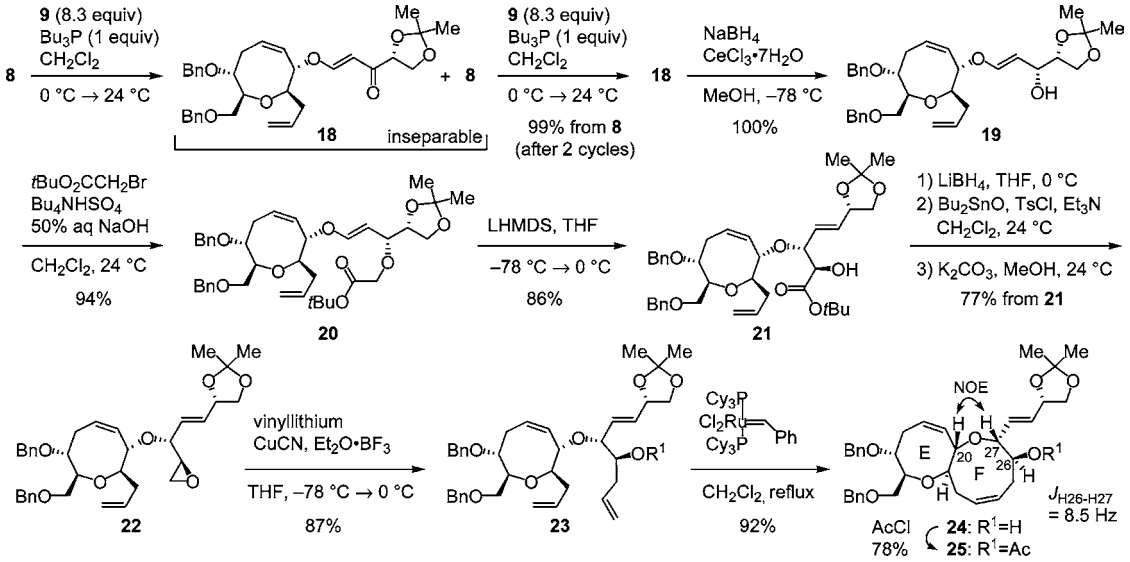
Scheme 3



Finally, RCM of **23** with first-generation Grubbs' catalyst[27] in refluxing CH_2Cl_2 furnished the desired **24** in high yield (92%). Remarkably, metathesis proceeded only between the two vinyl groups of **23** despite the presence of four reactive olefinic bonds. The stereochemistry at C26 and C27 of **24**, introduced during the [2,3]-Wittig rearrangement, was confirmed by ^{1}H NMR analysis after acetylation of **24**. The NOE between H20 and H27 and large $J_{H26-H27}$ (8.5 Hz) showed the 20,27-cis-26,27-trans configuration of **24**. Thus, stereoselective construction of the F-ring was achieved in nine steps in 50% overall yield from **8**.

In conclusion, the EF-ring segment (**24**) of **1** was efficiently synthesized from **8** through a key process including 1,4-addition, chirality-transferring *anti*-selective [2,3]-Wittig rearrangement, and RCM. Further studies toward the total synthesis of **1** are in progress in this laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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