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Synthesis of the common FGHI-ring part of ciguatoxins

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Abstract—The common FGHI-ring part (**2**) of ciguatoxins has been synthesized from the F- and I-ring parts (**6** and **5**, respectively). The Nozaki–Hiyama–Kishi coupling of **6** with **5** followed by regio- and stereoselective epoxidation at C29 and C30 afforded an epoxide (**4**), which was transformed into a tricyclic compound (**3**) corresponding to the F-HI-ring part by 6-*exo*-epoxide opening and the subsequent inversion of the C29 stereocenter. Reductive cyclization of **3** forming the C31–O26 bond of the G-ring successfully produced **2**.

Ciguatoxins,[1] characterized by potent neurotoxicity due to strong activation of the voltage-sensitive sodium channels (VSSC),[2] were isolated as causative toxins of ciguatera fish poisoning.[3] They have a ladder-shaped *trans*-fused polyether structure including 13 medium rings, such as ciguatoxin CTX3C (**1**)[1a] shown in Scheme 1. Since the structural complexity and the strong bioactivity have attracted the attention of chemists, ciguatoxins have been studied extensively in the synthetic view point.[4,5] So far, in the course of our program toward total synthesis of ciguatoxins,[6] we reported the syntheses of the ABCDE and IJKLM-ring parts of **1**[6k,o] as well as a method for the addition of the F-ring to the E-ring part of CTX1B,[1b,c] which would also be available for the CTX3C synthesis.[6m] Therefore, our recent efforts have been focused on the construction of the middle part of **1** from the left (ABCDEF-ring) and the right (IJKLM-ring) segments. Here, the convergent synthesis of the common FGHI-ring part (**2**) of ciguatoxins is described.

Our plan for the synthesis of **2** from the F- and I-ring parts (**6** and **5**, respectively) is outlined in Scheme 1. The G-ring of **2** was envisioned to be constructed from hydroxy ketone **3** by reductive cyclization forming the O26–C31 bond and the C31 stereocenter.[7,8] In the synthesis of **3**, establishment of the C30 quaternary stereocenter, closely related to the construction of the H-ring part, was an issue. Therefore, we planned to employ the 6-*exo*-epoxide-opening reaction of **4**[9] for the H-ring formation followed by inversion of the C29 stereocenter and oxidation at C31. The epoxide **4** was intended to be synthesized from *E*-iodoalkene **6** and aldehyde **5** via the Nozaki–Hiyama–Kishi reaction[10] followed by regio- and stereoselective epoxidation. Both **5** and **6** would be prepared from the previously reported medium-ring ethers.[6h,o]

Preparation of the I-ring part **5** from known **7**[6h,o] is illustrated in Scheme 2. Although direct PMB protection of the hydroxy group at C34 of **7** was possible, the resulting compound resisted the removal of the benzylidene acetal without detachment of the PMB group. Therefore, alcohol **7** was first transformed into pivaloate **8** (100%), which was converted to PMB ether **13** (overall 73%) by a five-step process [(i) removal of the benzylidene acetal with $Zn(OTf)_2$/ethanedithiol,[6m,11] (ii) protection of the resulting diol with 4-bromobenzyl (PBB) bromide, (iii) detachment of the pivaloyl (Piv) group, (iv) PMB-protection of the resulting alcohol, (v) removal of the TBDPS group]. Oxidation of **13** with Dess–Martin periodinane (DMPI)[12] followed by Wittig reaction afforded **14** (79%), which was hydrolyzed in the presence of $Hg(OAc)_2$ to produce **5** in good yield (95%).[13]

The F-ring part **6** was synthesized from known **15**[6h] (Scheme 3). Removal of the TBS groups of **15** (91%) followed by protection with BnBr (90%) provided **17**,

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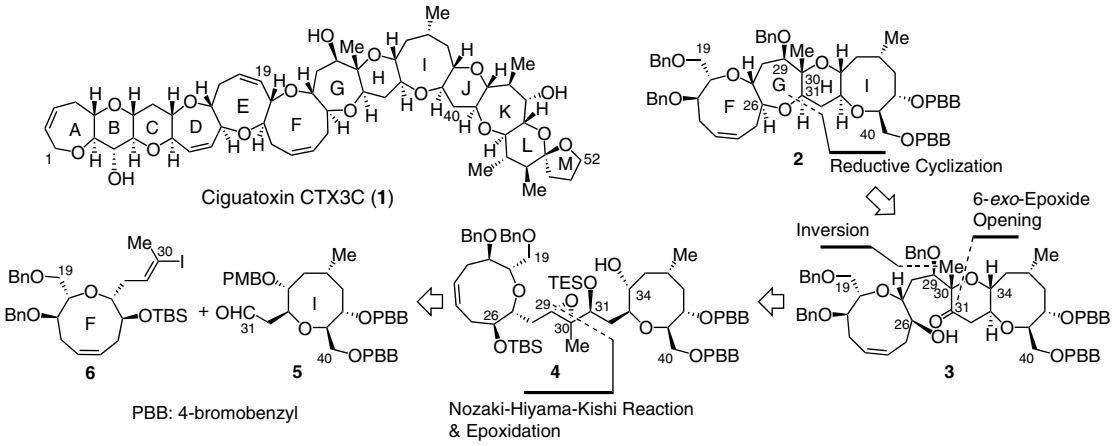
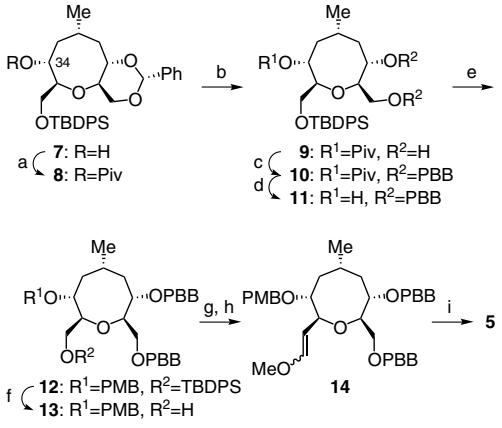
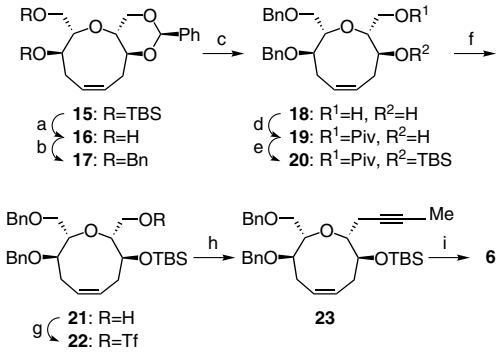


Scheme 1. Synthetic plan for the common FGHI-ring part (**2**) of ciguatoxins.



Scheme 2. Reagents and conditions: (a) PivCl, pyridine, 26 °C, 14 h, 100%; (b) $Zn(OTf)_2$, $HS(CH_2)_2SH$, $NaHCO_3$, CH_2Cl_2, 0 to 25 °C, 2 h, 88%; (c) PBBBr, NaH, Bu_4NI, THF, 25 °C, 14 h, 100%; (d) DIBALH, CH_2Cl_2, −78 °C, 1.5 h, 88%; (e) PMBBr, NaH, Bu_4NI, THF, 26 °C, 21 h; (f) Bu_4NF, THF, 0 °C, 1.5 h, 94% from **11**; (g) DMPI, CH_2Cl_2, 0 to 23 °C, 50 min; (h) $Ph_3P^+CH_2OMeCl^-$, NHMDS, 0 °C, 30 min, then aldehyde, −78 to 25 °C, 17 h, 79%; (i) $Hg(OAc)_2$, THF–H_2O (10:1), 23 °C, 1 h, then Bu_4NI, 1.5 h, 95%.

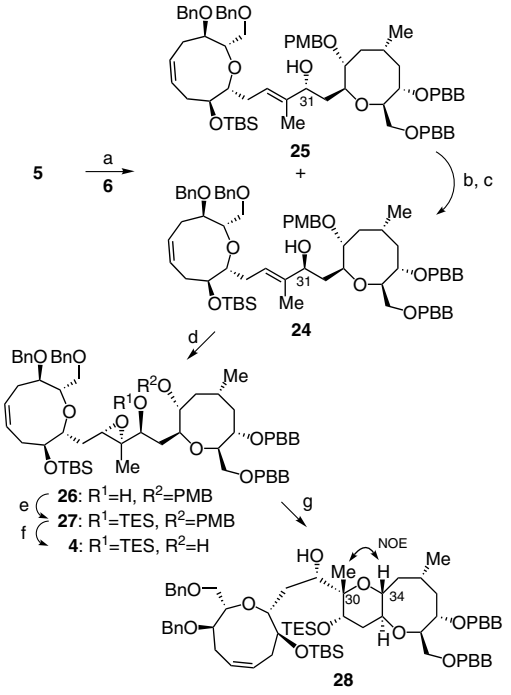


Scheme 3. Reagents and conditions: (a) Bu_4NF, THF, 25 °C, 11 h, 91%; (b) BnBr, NaH, Bu_4NI, THF, 26 °C, 5 h, 90%; (c) 3 M HCl aq–THF (1:1), 23 °C, 21 h, 98%; (d) PivCl, pyridine, 25 °C, 33 h, 80%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 97%; (f) DIBALH, CH_2Cl_2, −78 °C, 2 h, 99%; (g) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 96%; (h) propyne, BuLi, THF, −78 °C, 15 min, then **22**, −78 to 25 °C, 3 h, 97%; (i) Cp_2ZrCl_2, DIBALH, THF, 55 °C, 30 min, then I_2, 0 °C, 15 min, 86%.

which was hydrolyzed to give **18** (98%). The primary alcohol of **18** was selectively protected with PivCl (80%), and the resulting **19** was transformed into **21** (overall 96%) by a two-step TBS-protection/Piv-detachment process. Conversion of **21** to triflate **22** (96%) and the subsequent reaction with 1-propynyllithium (97%) afforded **23**,[14] which was treated first with a zirconium reagent, prepared from Cp_2ZrCl_2 and DIBALH,[15] and then with I_2 to produce **6** regioselectively (86%).

Connection of **5** and **6** as well as construction of the H-ring is depicted in Scheme 4. According to the Nozaki–Hiyama–Kishi procedure,[10] the segments **5** and **6** were treated with $CrCl_2$ in the presence of $NiCl_2$ (0.5 wt.% of $CrCl_2$) in DMSO, and the reaction smoothly proceeded to give **24** (45% from **5**) and its C31-epimer **25** (40% from **5**) in good yield.[16] The epimer **25** could be transformed into **24** in good yield and selectivity (overall 100%, **24**:**25** = 13:1) through oxidation with Dess–Martin periodinane (DMPI) followed by reduction with L-Selectride®.[17] The $VO(acac)_2$-catalyzed epoxidation of **24** with TBHP exclusively afforded **26** (91%),[18] which was subjected to a protection/deprotection sequence to produce **4** (overall 95%). The hydroxy epoxide **4** was smoothly cyclized with catalytic CSA into **28** (80%). The stereochemistry at C30 of **28** was confirmed by the presence of NOE between H34 and the protons of the methyl group at C30. Thus, the I-ring **5** and the F-ring **6** were efficiently assembled into the F-HI-ring part **28** in overall 57% yield for total seven steps from **5**.

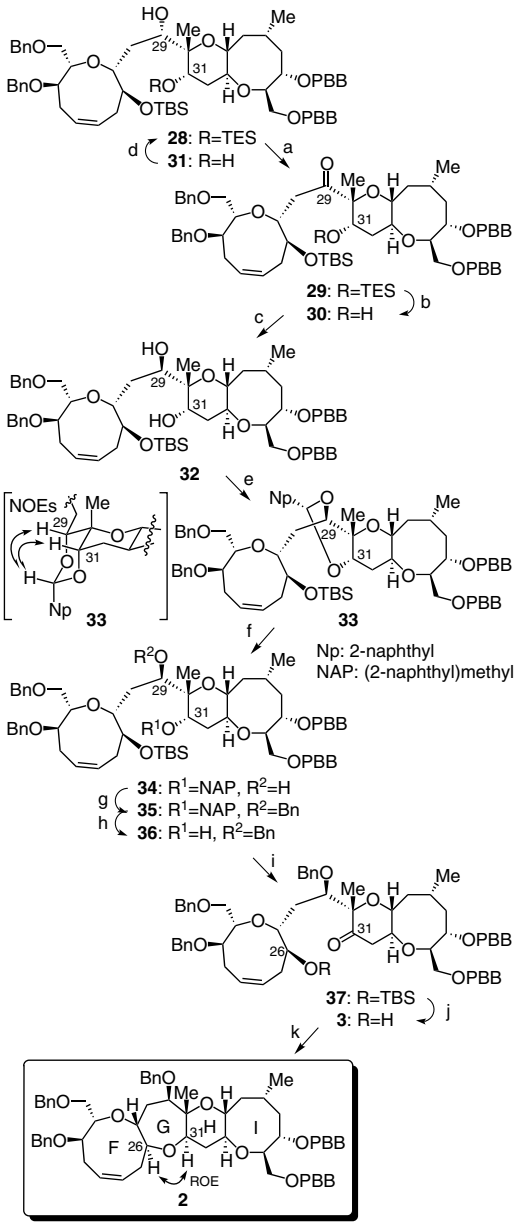
The synthesis of **2** from **28** is shown in Scheme 5. First, inversion of the stereochemistry at C29 of **28** was performed by an oxidation/reduction process. Although alcohol **28** resisted several oxidation reactions due to steric hindrance around the hydroxy group at C29, Swern oxidation[19] of **28** at higher temperature (−45 °C) for prolonged reaction time (1 h) was able to produce an inseparable ~5:1 mixture of ketone **29** and unreacted **28** in a good material balance (100%). The reduction of **29** to C29-*epi*-**28** was not achieved in spite of several attempts. Therefore, the reduction after detachment of the TES group at O31 was then investigated. Treatment of the mixture of **29** and **28** with HF·Py slowly afforded



Scheme 4. Reagents and conditions: (a) **6** (3.7 equiv), $CrCl_2$ (10 equiv), $NiCl_2$ (0.5 wt.% of $CrCl_2$), DMSO, 25 °C, 30 h, **24**: 45% from **5**, **25**: 40% from **5**; (b) DMPI, $NaHCO_3$, CH_2Cl_2, 25 °C, 2.5 h, 100%; (c) L-Selectride®, THF, −78 °C, 2 h, 100% (**24**:**25** = 13:1); (d) $VO(acac)_2$ (0.09 equiv), TBHP, toluene, 0 °C, 2 h, 91%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 10 min, 100%; (f) DDQ, CH_2Cl_2–pH 7 buffer (10:1), 0 °C, 1 h, 95%; (g) CSA (0.1 equiv), CH_2Cl_2, 0 °C, 25 min, 80%.

an inseparable ~5:1 mixture of hydroxy ketone **30** and diol **31** (75%) along with a mixture of recovered **29** and **28** (~5:1, 25%). The reduction of the mixture of **30** and **31** with $NaBH_4$ gave the desired diol **32** in 39% yield along with **31** in 35% yield.[20] The diol **31** was selectively protected with TESOTf to provide **28** in quantitative yield, thereby establishing the route for recycling undesired **31**. Next, selective but stepwise Bn protection at O29 of **32** was executed. The diol **32** was exclusively transformed into (2-naphthyl)methylene acetal **33**. The configurations at C29 and the acetal carbon of **33** were confirmed by the presence of NOEs between the acetal proton and H31 and between the acetal proton and H29. Reduction of **33** with DIBALH exclusively afforded (2-naphthyl)methyl (NAP)[21] ether **34**, which was quantitatively converted to the requisite **36** through a sequence of Bn protection at O29 and NAP deprotection at O31. Alcohol **36** was oxidized with DMPI[12] and the resulting **37** was desilylated to give **3** quantitatively. The reductive cyclization of **3** with excess Et_3SiH in the presence of TMSOTf at 0 °C produced **2** stereoselectively (64%).[7] The stereochemistry of **2** was confirmed by the presence of ROE between H26 and H31 as well as the large $J_{H31–H32ax}$ (12.1 Hz). Thus, the FGHI-ring part **2**[22] was successfully constructed from the F-ring **6** and the I-ring **5** in 9.5% overall yield over 17 steps including the transformation steps from **25** to **24**.

In conclusion, for the synthesis of the common FGHI-ring part (**2**) of ciguatoxins, a method based on the



Scheme 5. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −45 °C, 1 h, then Et_3N, 0 °C, 15 min, **28**+**29**: ~100% (**28**:**29** = 1:~5); (b) HF·Py, THF–Py (3:1), 23 °C, 7 d, **28**+**29**: 25% (**28**:**29** = 1:~5), **30**+**31**: 75% (**30**:**31** = ~5:1); (c) $NaBH_4$, MeOH, 0 °C, 20 min, **32**: 39%, **31**: 35%; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, −40 °C, 15 min, ~100%; (e) 2-naphthaldehyde dimethylacetal, PPTS, PhH, reflux, 2 h, 89%; (f) DIBALH, CH_2Cl_2, 0 °C, 4 h, ~100%; (g) BnBr, NaH, Bu_4NI, THF, 23 °C, 20 h, ~100%; (h) DDQ, CH_2Cl_2–pH 7 buffer (10:1), 0 °C, 20 min, ~100%; (i) DMPI, $NaHCO_3$, CH_2Cl_2, 23 °C, 25 min, ~100%; (j) HF·Py, THF, 23 °C, 2 d, ~100%; (k) TMSOTf, Et_3SiH–CH_2Cl_2 (1:10), 0 °C, 35 min, 64%.

Nozaki–Hiyama–Kishi reaction connecting the F-ring with the I-ring, regio- and stereoselective epoxidation, the 6-*exo*-epoxide opening reaction forming the H-ring, inversion of the C29 stereocenter, and reductive cyclization constructing the G-ring was successfully developed. Further studies toward the total synthesis of ciguatoxins are now in progress in this laboratory.

Acknowledgements

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20. The net product ratio of **32** to **31** from **30** was determined as 2:1 by the reduction of pure **30**, prepared alternatively, under the same conditions.
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22. Selected spectral data of **2**: $[\alpha]_D^{23}$ −5.0 (*c* 0.025, $CHCl_3$); ^1H NMR (600 MHz, C_6D_6, C_6HD_5 as 7.15 ppm), δ 7.45 (2H, d, $J = 7.3$ Hz), 7.21–7.02 (17H, m), 6.94 (2H, d, $J = 8.1$ Hz), 6.83 (2H, d, $J = 8.1$ Hz), 5.93 (1H, dt, $J = 6.4$, 10.0 Hz), 5.82 (1H, dt, $J = 5.4$, 10.0 Hz), 4.85 (1H, d, $J = 12.1$ Hz), 4.71 (1H, d, $J = 12.1$ Hz), 4.39 (1H, d, $J = 12.3$ Hz), 4.37 (2H, s), 4.25 (1H, d, $J = 12.9$ Hz), 4.22 (1H, d, $J = 12.9$ Hz), 4.21 (1H, d, $J = 11.7$ Hz), 4.11 (1H, d, $J = 12.3$ Hz), 3.87 (1H, d, $J = 11.7$ Hz), 3.70 (1H, t, $J = 6.0$ Hz), 3.66–3.53 (6H, m), 3.52–3.50 (1H, m), 3.49–3.47 (1H, m), 3.39 (1H, dd, $J = 7.1$, 9.9 Hz), 3.26–3.20 (2H, m), 3.07 (1H, dd, $J = 4.6$, 12.1 Hz), 2.94 (1H, ddd, $J = 5.0$, 10.0, 13.9 Hz), 2.69–2.63 (2H, m), 2.40 (1H, dt, $J = 12.5$, 4.6 Hz), 2.31–2.26 (3H, m), 2.00–1.84 (4H, m), 1.68–1.57 (2H, m), 1.44 (3H, s), 1.00 (3H, d, $J = 7.3$ Hz); ^{13}C NMR (125 MHz, C_6D_6, $^{13}CC5D6$ as 128.0 ppm) δ 11.9 (CH_3), 26.9 (CH_3) 27.9 (CH_2), 28.6 (CH), 33.1 (CH_2), 36.2 (CH_2), 38.8 (CH_2), 39.8 (CH_2), 45.5 (CH_2), 70.3 (CH_2), 71.0 (CH_2), 72.5 (CH+$CH_2 \times 3$), 73.3 ($CH_2 \times 2$), 79.0 (CH), 79.6 (CH × 2), 80.8 (C), 82.3 (CH), 83.1 (CH), 83.6 (CH), 85.0 (CH × 2), 86.0 (CH), 121.4 (C × 2), 127.8 (CH × 6), 128.2 (CH × 2), 129.3 (CH × 4), 131.5 (CH × 4), 137.8 (C × 2), 138.9 (C × 2), 140.2 (C) (The signals of nine carbons of Bn groups were undetected due to overlapping with solvent signal); IR (film) ν_{max} 2954, 2923, 2853, 1594, 1487, 1462, 1376, 1287, 1260, 1204, 1096, 1070, 1027, 1012, 840, 803, 729, 697 cm^{-1}; HR-FDMS, calcd for $C_{59}H_{68}{}^{79}Br_2O_9$ [M^+]: 1078.3230, found: 1078.3217.