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A concise route to the right wing of ciguatoxin

Atsushi Tatami, Masayuki Inoue,* Hisatoshi Uehara and Masahiro Hirama*

Department of Chemistry, Graduate School of Science, Tohoku University, and SORST, Japan Science and Technology Corporation (JST), Sendai 980-8578, Japan

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Abstract—A concise route to the HIJKLM-ring fragment **10** of ciguatoxin (CTX) and 51-hydroxyCTX3C was developed in which oxiranyl anion addition and intramolecular carbonyl olefination were utilized as key transformations. The present procedure requires only 23 steps from the I-ring **5**, while 35 steps were employed in a previous synthesis of the corresponding right wing **11** of CTX3C. The high efficiency of the present synthesis ensures a supply of **10** for total synthesis and biomedical applications.

Many tropical species of fish may cause an intoxication known as ciguatera.[1] The causative toxins, ciguatoxins,[2] originate in epiphytic dinoflagellates *Gambierdiscus toxicus*, and subsequently enter the food chain.[3] Dinoflagellate toxins, such as CTX3C (**1**, Fig. 1)[2d] and CTX4B **3**,[2a,b] undergo oxidation in fish, yielding more toxic products, for instance, 51-hydroxyCTX3C **2**[2e] and ciguatoxin (CTX, **4**).[2a,b] Upon ingestion, these potent neurotoxins target voltage-sensitive sodium channels, and cause persistent activation of these channels.[4] Because the presence of these toxins in fish is unpredictable, a sensitive immunochemical method for detecting ciguatoxins has long been necessary.[5] Very recently, we achieved the first practical total synthesis of CTX3C **1**,[6,7] and developed an immunoassay for **1** by utilizing synthetic haptens,[8] which has paved the way for biomedical research on ciguatoxins.

The final stage of our synthesis of **1** involved coupling between the left and right wings with subsequent construction of the central FG-ring system.[6,9] This strategy is applicable to all ciguatoxins, because they share the FG-ring structure.[2] To synthesize structural variants of ciguatoxins for antibody-preparations and detailed SAR, we selected oxidized ciguatoxins (**2**, **4**) as important targets. In this paper, we describe the concise synthesis of the NAP-protected[10] right wing **10** of **2** and **4** by applying a significantly improved protocol (Scheme 1).

In the previous synthesis of the right half of CTX3C (**11**, Scheme 1), while the IJKLM-ring segment **6** was constructed from the I-(**5**) and LM-ring segments in a convergent manner, the subsequent attachment of the H-ring to **6** required 20 synthetic steps.[11] To facilitate

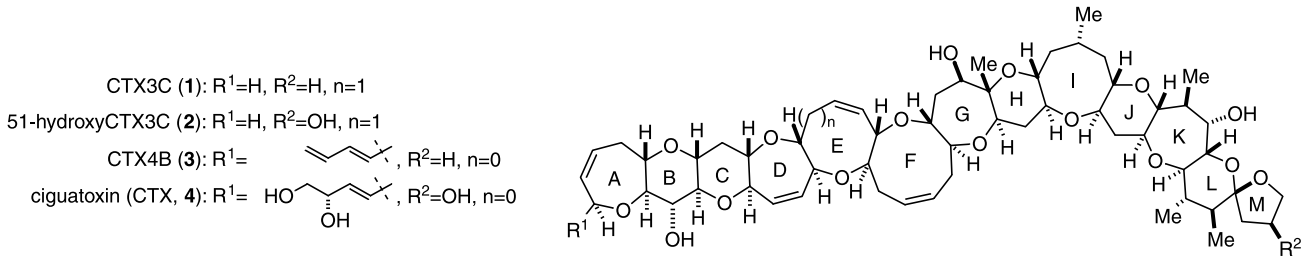

Figure 1. Structures of ciguatoxins.

Keywords: convergent synthesis; intramolecular carbonyl olefination; low-valent titanium complex; polyether; ciguatoxin; 51hydroxy-CTX3C.
* Corresponding authors. Fax: +81-22-217-6566; e-mail: inoue@ykbsc.chem.tohoku.ac.jp; hirama@ykbsc.chem.tohoku.ac.jp

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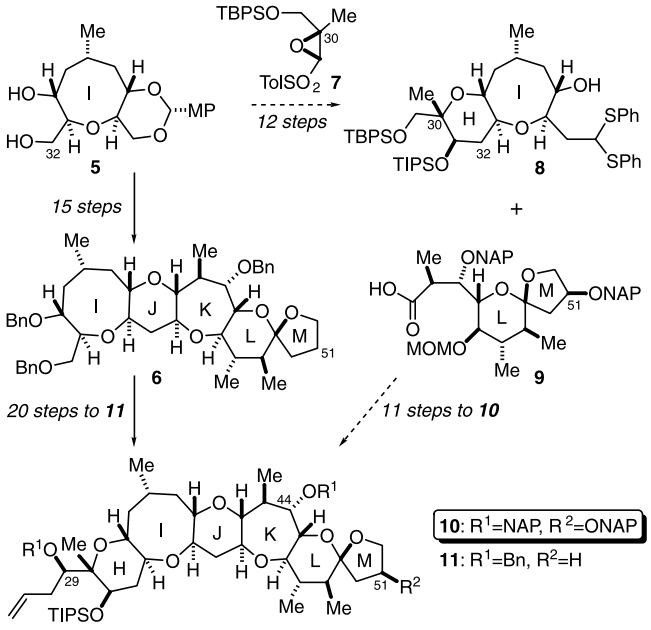
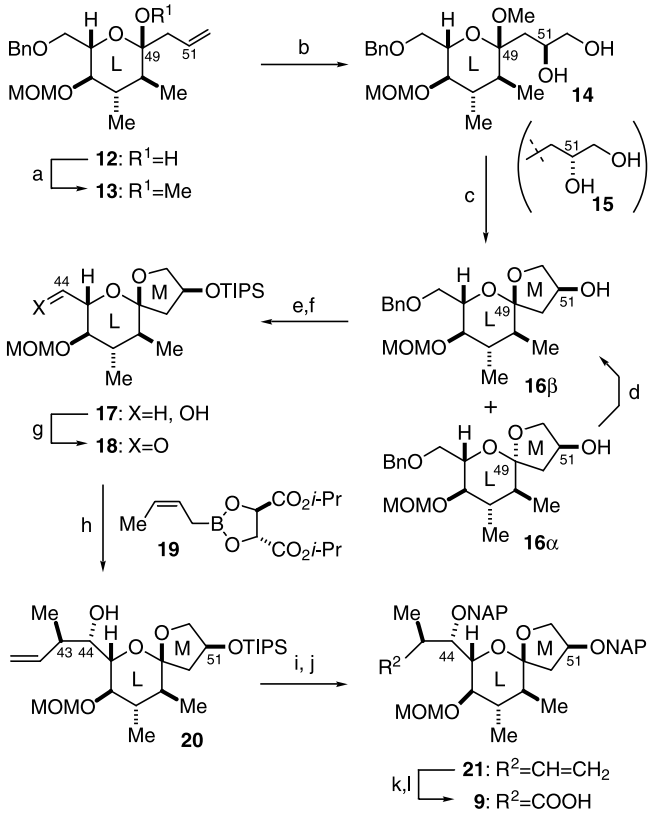


Scheme 1. Synthesis plan of the right wing of ciguatoxin and 51-hydroxyCTX3C.

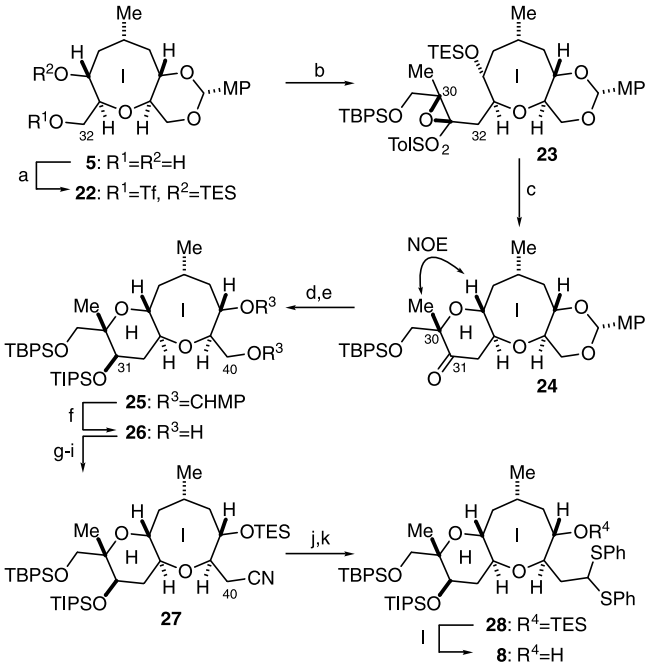
H-ring construction for **10**, the four-carbon unit **7** was planned to be directly introduced via the oxiranyl anion strategy developed by Mori.[12] Additionally, the H-ring was to be built on the I-ring fragment (**5**→**8**) instead of the IJKLM-ring system in order to maximize the synthetic convergency and minimize the protective group manipulations.

Synthesis of the LM-ring fragment **9** began with the previously reported olefin **12** (Scheme 2).[11,13,14] After conversion of hemiacetal **12** to methylacetal **13** (94%), the 51-OH group was installed by Sharpless asymmetric dihydroxylation using $(DHQ)_2PYR$,[15] which led to the desired diol **14** as the major diastereomer (**14**:**15**= 4:1, 97% yield). Intramolecular *trans*-acetalization of the isolated **14** with CSA generated five-membered spiroacetals favoring the requisite stereoisomer **16β** (**16α**:**16β**=1:2, 90% yield). The separated epimer **16α** was subjected to thermodynamic equilibration to yield the same ratio of the diastereomers. The secondary alcohol of the combined spiroacetal **16β** was temporarily masked with TIPS, and the benzyl group was then removed by hydrogenolysis to provide the primary alcohol **17** (96% for two steps). After oxidation of **17**, addition of Roush's crotyl boronate **19**[16] to aldehyde **18** set the two stereocenters (C43, C44), giving rise to **20** with complete stereochemical control (69% for 2 steps). Removal of the TIPS group from **20** and introduction of the NAP group produced the bis-NAP ether **21** in 99% yield. Finally, oxidative cleavage of the terminal olefin of **21**, followed by oxidation to the carboxylic acid, led to LM-ring fragment **9** in 82% yield for the two steps.

The coupling partner of **9**, the HI-ring fragment **8**, was prepared from the known I-ring **5**[11] using Mori's oxiranyl anion strategy (Scheme 3).[12] Diol **5** was converted to the protected triflate **22** by stepwise addition of Tf_2O and TESOTf in the presence of base and molecular sieves. A mixture of the resultant **22** and epoxysulfone **7**[12d] in THF–HMPA was treated with *n*-BuLi at −110°C for 30 min, leading to the formation of the desired coupling adduct **23**. Then, 6-*endo* cyclization to construct the H-ring was realized by submitting **23** to *p*-TsOH in CH_2Cl_2 with *p*-methoxybenzylidene methylacetal[17] to afford the bicyclic fused ether **24** through concomitant removal of TES (46% from **5**). Thus, obtained **24** was reduced using $NaBH_4$, and the newly formed alcohol was protected as its TIPS ether to give **25** as the sole product in quantitative yield (two steps). After acid-promoted removal of the MP acetal from **25**, one-carbon exten-



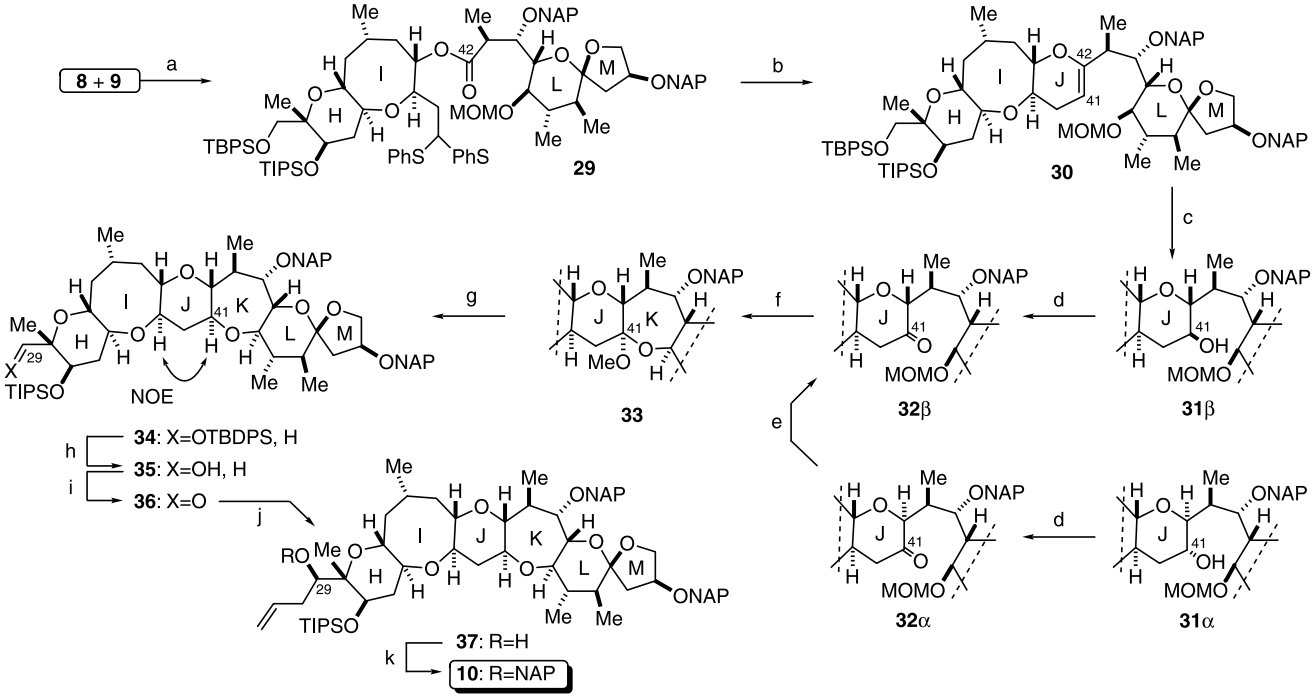
Scheme 2. *Reagents and conditions*: (a) $(MeO)_3CH$, CSA, $(CH_2Cl)_2$, rt, 94%; (b) OsO_4, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0°C, 97% (**14**:**15**=4:1); (c) CSA, $(CH_2Cl)_2$, rt, 90% (**16α**:**16β**=1:2); (d) PPTS, PhH/$(CH_2Cl)_2$ (1:1), 60°C, 75% (**16α**:**16β**=1:2); (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 96%; (f) $Pd(OH)_2/C$, H_2, EtOAc, rt, 100%; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N; (h) **19**, 4 Å MS, toluene, −78°C, 69% (two steps); (i) TBAF, THF, rt; (j) NAPBr, TBAI, NaH, THF/DMF (3:1), 0°C to rt, 99% (two steps); (k) OsO_4, NMO, *t*-BuOH/H_2O (1:1), rt, then $NaIO_4$; (l) $NaClO_2$, $NaPO_4{\cdot}H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), 82% (two steps).



Scheme 3. *Reagents and conditions*: (a) Tf_2O, 2,6-lutidine, 4 Å MS, CH_2Cl_2, then TESOTf, −78°C; (b) **7**, *n*-BuLi, HMPA, THF, −110°C; (c) $TsOH{\cdot}H_2O$, CH_2Cl_2, $(MeO)_2CH$(*p*-MeOPh), 0°C to rt, 46% (three steps); (d) $NaBH_4$, CH_2Cl_2/MeOH (1:1), −78°C, 100%; (e) TIPSOTf, 2,6-lutidine, $(CH_2Cl)_2$, 50°C, 100%; (f) TFA/THF/H_2O (1:10:5), rt, 87%; (g) Ph_3P, I_2, imidazole, 4 Å MS, THF, −30 to 0°C, 87%; (h) NaCN, DMSO, 40°C, 97%; (i) TESOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 100%; (j) DIBAL, CH_2Cl_2, −78°C; (k) PhSSPh, n-Bu_3P, 40°C, 83% (two steps); (l) PPTS, MeOH/CH_2Cl_2 (5:1), 0°C, 84%.

sion of **26** at the primary alcohol via a two-step sequence, followed by the TES protection of the secondary alcohol, resulted in nitrile **27** in 73% yield from **25**. Then, **27** was reduced to the corresponding aldehyde, which was converted to dithioacetal **28** using phenyldisulfide and PBu_3 (83% yield, two steps).[18] For the next coupling reaction, the TES group of the tris-silylated **28** was selectively removed using PPTS in MeOH–CH_2Cl_2 at 0°C to produce the HI-ring alcohol **8** in 84% yield.

Having synthesized both fragments, the coupling and subsequent construction of the JK-ring were pursued (Scheme 4). Condensation of alcohol **8** and carboxylic acid **9** using the Yamaguchi protocol[19] gave the corresponding ester **29** in 77% yield. Cyclization of the J-ring from **29** was then achieved by intramolecular carbonyl olefination using the low-valent titanium reagent developed by Takeda,[20] which successfully closed the six-membered J-ring to afford **30** in 68% yield.[11] Hydroboration of enol ether **30** installed an alcohol at C41 to generate a separable mixture of **31α** (57%) and **31β** (19%), both of which were separately oxidized with Dess–Martin periodinane into ketones **32α** and **32β**, respectively. The undesired isomer **32α** was effectively converted to **32β** by three cycles of the DBU-mediated isomerization–separation sequence in 66% yield. Combined **32β** was then exposed to trifric acid and $(MeO)_3CH$ in hexane, directly leading to seven-membered methylacetal **33** via loss of the MOM group (62% yield). Reductive etherification[21] of acetal **33** using Et_3SiH and $BF_3{\cdot}OEt_2$ in the presence of molecular sieves constructed the last ether ring to afford the HIJKLM-ring system **34** in 78% yield, whose NOE experiment verified the selective attack of hydride from



Scheme 4. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP, 35°C, 77%; (b) $Cp_2Ti[P(OEt)_3]_2$, THF, reflux, 68%; (c) $BH_3{\cdot}SMe_2$, THF, 0°C to rt then NaOH, H_2O_2, 76% (**31α**:**31β** = 3:1); (d) Dess–Martin periodinane, CH_2Cl_2, rt, 90% for **32α**, 97% for **32β**; (e) DBU, CH_2Cl_2, rt, 66% (three cycles, 12% of **32α** was recovered); (f) TfOH, $(MeO)_3CH$, hexane, rt, 62%; (g) $BF_3{\cdot}OEt_2$, Et_3SiH, 4 Å MS, CH_2Cl_2, −50 to −20°C, 78%; (h) HF·Py, Py/THF (1:2), rt, 76%; (i) $SO_3{\cdot}Py$, Et_3N, DMSO/CH_2Cl_2 (1:2), 0°C to rt; (j) allylSnBu$_3$, $MgBr_2{\cdot}OEt_2$, 4 Å MS, toluene, −78°C to rt, 62%, C29-epimer 21% (two steps); (k) NAPBr, TBAI, NaH, THF/DMF (3:1), rt, 91%.

the α-face of the molecule. In this way, the JK-ring was assembled from the fragments (**8**, **9**) through only seven synthetic operations.

To complete the synthesis of the right wing of CTX, the carbon chain corresponding to the G-ring was introduced (Scheme 4). HF·pyridine effected the selective removal of TBPS to afford **35** in 76% yield. The alcohol of **35** was in turn oxidized with SO_3·pyridine to aldehyde **36**, which was subjected to $MgBr_2$-promoted allylation using allyltributylstannane to generate alcohol **37** (62%) and the C29-epimer (21%). Finally, NAP protection of **37** gave rise to the targeted right wing **10** in 91% yield, which can be readily coupled with the left wing after modification of the terminal olefin.[6,9,22]

In conclusion, the right half of CTX and 51-hydroxy-CTX3C was synthesized by a highly convergent strategy using a significantly improved protocol. The present synthesis of **10** only requires 23 steps from I-ring **5**, whereas the previous procedure for **11** involved 35 steps.[11] Of note in the present synthesis is the successful application of the oxiranyl anion strategy for the H-ring and the intramolecular carbonylation protocol for the J-ring, both of which substantially contributed to the conciseness of the synthesis. The total syntheses of ciguatoxin and 51-hydroxyCTX3C have become our next focus, and will be reported in due course.

Acknowledgements

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22. Physical data for **10**: $[\alpha]_D^{22}$ 2.30 (*c* 0.39, $CHCl_3$); IR (film) 2943, 2866, 1459, 1090, 1031, 815, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01–1.11 (33H, m, TIPS, Me54, Me55, Me56, Me57), 1.14 (3H, s, Me53), 1.37 (1H, q, $J=11.5$ Hz, H40), 1.50–1.63 (3H, m, H35, 37, 47), 1.72 (1H, q, $J=11.5$ Hz, H32), 1.80–1.89 (4H, m, H35, H36, H37, H48), 2.10 (1H, dt, $J=11.5$, 5.5 Hz, H40), 2.13–2.22 (4H, m, H32, H43, H50×2), 2.49–2.58 (2H, m, H28×2), 2.85 (1H, dd, $J=9.5$, 4.5 Hz, H42), 2.99 (1H, ddd, $J=11.5$, 9.5, 2.0 Hz, H38), 3.04–3.12 (2H, m, H33, H39), 3.30 (1H, dt, $J=9.5$, 3.5 Hz, H34), 3.42 (1H, t, $J=9.5$ Hz, H46), 3.43 (1H, d, $J=3.5$ Hz, H44), 3.62 (1H, d, $J=9.5$ Hz, H45), 3.66 (1H, dd, $J=8.0$, 4.5 Hz, H29), 3.82 (1H, dd, $J=9.5$, 5.0 Hz, H52), 3.85 (1H, ddd, $J=11.5$, 9.5, 5.5 Hz, H41), 3.98 (1H, dd, $J=9.5$, 1.5 Hz, H52), 4.26 (1H, dd, $J=11.5$, 5.0 Hz, H31), 4.27 (1H, br, H51), 4.59 (1H, d, $J=12.0$ Hz, NAP), 4.62 (1H, d, $J=12.0$ Hz, NAP), 4.74 (1H, d, $J=12.5$ Hz, NAP), 4.75 (1H, d, $J=12.5$ Hz, NAP), 4.81 (1H, d, $J=11.0$ Hz, NAP), 4.84 (1H, d, $J=11.0$ Hz, NAP), 5.01 (1H, dd, $J=10.5$, 2.0 Hz, H26), 5.12 (1H, dd, $J=17.0$, 1.5 Hz, H26), 5.99 (1H, ddt, $J=17.0$, 10.5, 6.5 Hz, H27), 7.41–7.83 (21H, m, NAP×3); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 13.3, 13.8, 14.2, 14.3, 16.2, 18.57, 18.59, 20.1, 27.8, 28.3, 29.6, 29.9, 31.8, 32.1, 33.5, 38.6, 38.7, 40.4, 40.8, 41.8, 42.7, 45.7, 46.2, 68.6, 71.4, 71.70, 71.77, 72.1, 72.4, 73.7, 74.4, 78.0, 78.8, 80.2, 81.1, 82.2, 83.2, 83.3, 84.8, 86.9, 109.2, 116.1, 125.6, 125.90, 125.93, 126.01, 126.03, 126.05, 126.1, 126.2, 126.32, 126.38, 126.39, 126.5, 127.8, 127.94, 127.97, 128.00, 128.07, 128.09, 128.42, 132.9, 133.1, 133.2, 133.4, 133.5, 135.9, 137.0, 137.3, 137.5; MALDI-TOF MS calcd for $C_{74}H_{96}NaO_{10}Si$ ($M+Na^+$) 1195.67 found 1195.66.