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Convergent synthesis of the IJKLM-ring part of ciguatoxin CTX3C

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Abstract—Convergent synthesis of the IJKLM-ring part (**2**) of ciguatoxin CTX3C has been achieved from the I-ring and the L-ring parts (**4** and **5**) in total eight steps in 27% overall yield. The carbanion derived from **4**, stabilized by a dimethyldithioacetal *S*-oxide group, was readily reacted with aldehyde **5** to give an adduct, which was facilely transformed into the corresponding α,ε-dihydroxy ketone **3**. The JK-ring formation from **3** under reductive conditions followed by oxidative M-ring cyclization efficiently led to the pentacyclic ether **2**. Improved synthesis of **6**, a synthetic intermediate for **4**, was also established.

CTX3C (**1**)[1] was isolated as a congener of ciguatoxin (CTX)[2] from cultured dinoflagellate *Gambierdiscus toxicus* by the Yasumoto group. It shows potent neurotoxicity [ip LD_{50} (mouse): 1.3 μg/kg] by strong binding to voltage-sensitive sodium channels.[3] Its unique ladder-shaped polycyclic ether structure and strong bioactivity have attracted the attention of many synthetic chemists.[4,5] In the course of our studies directed toward the total synthesis of ciguatoxins,[6] we have developed a general method for the convergent construction of X/6/7/X ring systems and applied the method to the synthesis of the ABCDE-ring part of **1**.[6k] Herein, we describe an efficient synthesis of the IJKLM-ring part (**2**)[7] of **1** based on our established methodology.[6g]

We planned the synthesis of **2** from the I-ring part **4** and the L-ring part **5**[6n] via the same route as that previously established in the IJKL-ring model (Scheme 1).[6g] The dimethyldithioacetal mono-*S*-oxide group of **4** would be deprotonated facilely by an appropriate amide base to give an acyl anion equivalent,[8] which would be readily coupled with aldehyde **5**. The resulting adduct would be transformed to the corresponding α,ε-dihydroxy ketone **3**. The subsequent reductive hydroxy-ketone cyclization reactions[9] would construct the JK-ring part. The M-ring would be constructed through an intramolecular hydrogen abstraction–cyclization process at the final stage.[10] Although the I-ring part **6**, which would be a precursor of **4**, was previously synthesized from aldehyde **8** in total 17 steps,[6h] we also envisioned an alternative route to **6** from **8** via **7**, including a two-step ring-closing olefin metathesis (RCM)/stereoselective hydrogenation process, in order to improve the efficiency of the I-ring synthesis.

The synthesis of **4**, which includes the improved route to **6** from **8**, is shown in Scheme 2. Stereoselective methallylation of **8** by treatment with methallyltributyltin and dichlorodiisopropoxytitanium afforded homoallyl alcohol **9** as a major product (89%) along with a small amount of 34-*epi*-**9** (11%).[11] After deprotection of the TBS groups of **9** followed by oxidative cleavage, the resulting dialdehyde was reduced to triol **10** (85% overall yield). The 1,3-diol part of **10** was selectively protected as phenyl boronate to give alcohol **11** in quantitative yield, which was converted to diol **12** by a three-step process [(i) Dess–Martin oxidation;[12] (ii) Wittig reaction; (iii) removal of the phenyl boronate group] (67% overall yield). The primary hydroxy group of **12** was selectively protected as its TBDPS ether to give diene **7** in 90% yield. Ring closure of **7** in refluxing 1,2-dichloroethane by Grubbs' second-generation ruthenium catalyst[13] afforded olefin **13** (82% yield), which was hydrogenated stereoselectively using Crabtree's catalyst[14] to give eight-membered ether **6** in 80% yield (dr >20:1).[6h] Thereby, the improved synthesis of **6** from **8** was achieved in 10 steps in overall 34% yield.[15] Conversion of **6** to diol **14** was performed through a three-step protection/deprotection sequence [(i) removal of the TBDPS group; (ii) protection of the resulting diol as the benzyl ether; and (iii) removal of the benzylidene

Keywords: Ciguatoxin CTX3C; Natural product synthesis; Acyl anion equivalent; Reductive etherification; Spirocyclic acetal formation.
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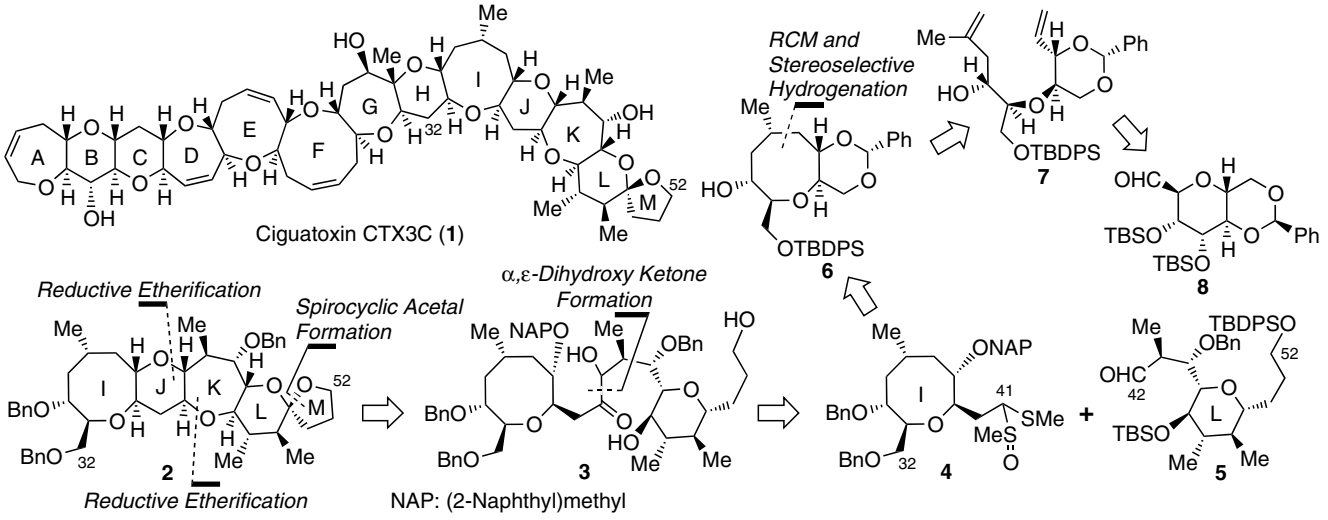
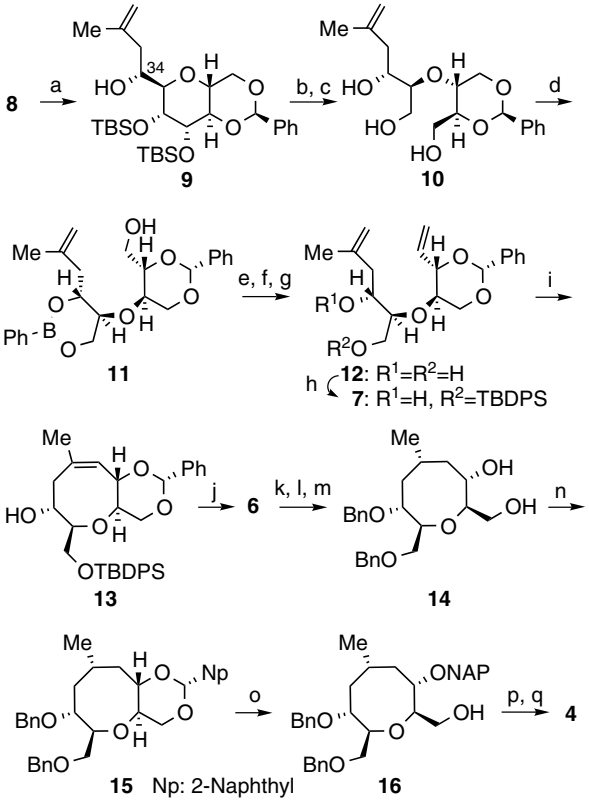


Scheme 1. Synthetic plan for the IJKLM-ring part (**2**) of CTX3C (**1**).



Scheme 2. Synthesis of the I-ring part **4**. Reagents and conditions: (a) $Bu_3SnCH_2C(CH_3)CH_2$, $TiCl_2(O^iPr)_2$, CH_2Cl_2, −78 °C, 2 h, **9**: 89%, 34-*epi*-**9**: 11%; (b) TBAF, THF, 23 °C, 12 h; (c) $NaIO_4$, 1,4-dioxane–H_2O (3:1), 23 °C, 1 h, then $NaBH_4$, MeOH, 0 °C, 1 h, 85% from **8**; (d) $PhB(OH)_2$, PhH, 23 °C, 30 min, 100%; (e) DMPI, CH_2Cl_2, 23 °C, 21 h; (f) Ph_3PCH_3Br, NHMDS, THF, 23 °C, 1 h, −78 → 23 °C, 2 h; (g) H_2O_2, EtOAc, 23 °C, 1 h, 67% from **10**; (h) TBDPSCl, imidazole, DMF, 23 °C, 30 min, 90%; (i) $(H_2IMes)(PCy_3)Cl_2RuCHPh$, $(CH_2Cl)_2$, reflux, 82%; (j) H_2, $[(cod)(py)(Cy_3P)Ir]PF_6$, CH_2Cl_2, 0 °C, 5 h, 80%; (k) TBAF, THF, 23 °C, 30 min; (l) BnBr, ^{t}BuOK, TBAI, THF, 23 °C, 30 min; (m) ethanedithiol, BF_3Et_2O, CH_2Cl_2, −20 °C, 30 min, 91% from **6**; (n) 2-naphthaldehyde, PPTS, benzene, reflux, 12 h, 93%; (o) $LiAlH_4$, $AlCl_3$, CH_2Cl_2–Et_2O (1:1), 23 °C, 2 h, 85%; (p) Tf_2O, 2,6-lutidine, CH_2Cl_2, −20 °C, 30 min; (q) $MeSCH_2S(O)Me$, NHMDS, THF, −20 °C, 15 min, 84% from **16**.

acetal group] (91% overall yield). Since diol **14** was obtained as colorless plates (mp 63–64 °C), the structure of **14** was established by X-ray crystallographic analysis (Fig. 1).[16] Diol **14** was treated with 2-naphthaldehyde to produce naphthylmethylene acetal **15** (93% yield), which was cleaved regioselectively using $LiAlH_4$–$AlCl_3$ to give primary alcohol **16** exclusively in 85% yield.[17] Transformation of **16** into the corresponding triflate ester and the subsequent substitution by the carbanion generated from methylthiomethyl methyl sulfoxide afforded **4** in 84% yield. Thus, the I-ring part **4** was synthesized from **8** in 17 steps in 18% overall yield.

Construction of the IJKLM-ring part **2** is depicted in Scheme 3. Deprotonation of **4** with LDA followed by the reaction with **5**[6n] (0.19 equiv) produced **17** as a mixture of diastereomers (98% yield from **5**, 81% recovery of **4**). The TBS, TBDPS, and methylthio methylsulfinyl acetal groups of **17** were removed under acidic conditions to give **3** (69% yield), which was cyclized by the treatment with Et_3SiH in the presence of TMSOTf into **18** as the sole stereoisomer in 73% yield.[9] After the

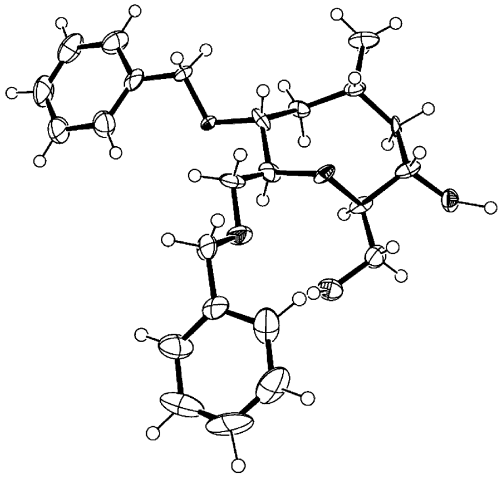
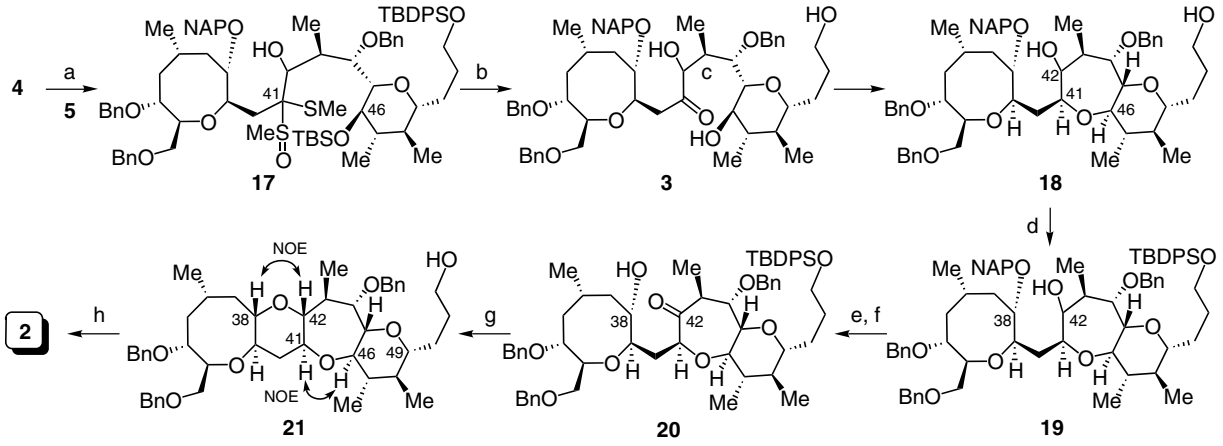


Figure 1. ORTEP diagram of **14**.



Scheme 3. Synthesis of the IJKLM-ring part **2**. Reagents and conditions: (a) **4**, LDA, THF, −20 °C, 15 min, then **5**, −78 °C, 30 min, 98%; (b) PTS, MeOH, 23 °C, 30 min, 69%; (c) TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C, 30 min, 73%; (d) TBDPSCl, imidazole, DMF, 23 °C, 30 min, 87%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 10 min; (f) DDQ, CH_2Cl_2—pH 7 buffer (10:1), 23 °C, 10 min; (g) TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C, 30 min, 86% from **19**; (h) $PhI(OAc)_2$, I_2, hv, cyclohexane, 23 °C, 3 h, then CSA, MeOH, 23 °C, 5 h, 73%.

protection of the primary hydroxy group of **18** as its TBDPS ether (87% yield), oxidation and the subsequent deprotection of the NAP group with DDQ afforded hydroxy-ketone **20**. Reductive cyclization of **20** with the concomitant detachment of the TBDPS group produced tetracyclic ether **21**[18] (86% overall yield). The presence of NOE (H41/H46 and H38/H42) in **21** confirmed that the newly formed stereocenters at the C41 and C42 positions had the desired stereochemistry. With the IJKL-ring part **21** in hand, oxidative radical cyclization of the M-ring was performed. Irradiation of a mixture of **21**, $PhI(OAc)_2$, and iodine in cyclohexane with a 60 W incandescent lamp successfully produced a 1:1 mixture of spirocyclic acetal **2** and its C49 epimer.[10] When the diastereomeric mixture was exposed to CSA in MeOH in order to perform isomerization, the spirocyclic acetal **2** was given as the sole product in 73% yield. The spectral data (^1H NMR and ^{13}C NMR) and optical rotation $\{[\alpha]_D^{23}$ −39.0 (*c* 0.070, $CHCl_3$); Lit.: $[\alpha]_D^{29}$ −41.2 (*c* 0.807, $CHCl_3$)[4d]$\}$ of **2** agreed well with those of the literature.[4d] Thus, the I- and L-ring parts (**4** and **5**) were convergently assembled into the IJKLM-ring part **2** in eight steps in 27% overall yield.

In conclusion, convergent synthesis of the IJKLM-ring part (**2**) of ciguatoxin CTX3C has been achieved from the I-ring and the L-ring parts (**4** and **5**). The carbanion derived from **4**, stabilized by a dimethyldithioacetal *S*-oxide group, was readily reacted with the aldehyde group of **5**. The resulting adduct **17** was facilely transformed to the corresponding α,ε-dihydroxy ketone **3**, which was efficiently transformed into the pentacyclic ether **2** by reductive etherification constructing the JK-ring part and the subsequent oxidative M-ring cyclization. Further studies toward the total synthesis of ciguatoxin CTX3C are now in progress in this laboratory.

Supplementary data

Crystallographic data (excluding structure factors) of **14** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 282748. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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15. In our previous route,[6h] cyclic ether **6** was synthesized from **8** in 17 steps in 34% overall yield. Although the overall yields of both new and old routes were equal, this new route, seven steps shorter than the previous route, saved time and labor.
16. Crystal data of **14**: $C_{24}H_{34}O_6$, *M* 418.53, monoclinic $P2_1$ (No. 4), $a = 12.785(6)$ Å, $b = 4.685(2)$ Å, $c = 19.814(9)$ Å, $\beta = 103.620(3)$, $U = 1153.4(9)$ Å^3, D_c ($Z = 2$) = 1.205 g/cm^3, $T = 153$ K, $\mu = 0.85$ cm^{-1}. The final *R* value is 0.052 for 2616 independent reflections with $I > 2\sigma I$ and 271 parameters.
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18. Selected spectral data of **21**: $[\alpha]_D^{23}$ −9.6 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6, C_6HD_5 as 7.15 ppm): δ 0.65 (3H, d, $J = 6.1$ Hz), 1.01 (3H, d, $J = 6.8$ Hz), 1.11–1.14 (6H, m), 1.14–1.23 (2H, m), 1.35–1.44 (1H, m), 1.55–1.81 (5H, m), 1.87–1.95 (2H, m), 2.05 (1H, br d, $J = 10.3$ Hz), 2.48 (1H, m), 2.68 (1H, dt, $J = 9.1$, 3.3 Hz), 2.85 (1H, br t, $J = 4.0$), 3.05 (1H, dd, $J = 4.8$, 9.2 Hz), 3.16 (1H, dt, $J = 1.5$, 7.5 Hz), 3.28 (1H, m), 3.30 (1H, br d, $J = 9.6$ Hz), 3.37 (1H, dt, $J = 1.5$, 6.3 Hz), 3.59 (1H, t, $J = 9.6$ Hz), 3.48–3.74 (5H, m), 4.09 (1H, m), 4.12 (1H, d, $J = 11.8$ Hz), 4.35–4.46 (3H, m), 4.67 (1H, d, $J = 12.0$ Hz), 4.72 (1H, d, $J = 12.0$ Hz), 7.04–7.65 (15H, m); ^{13}C NMR (75 MHz, C_6D_6, $^{13}CC_5D_6$ as 128.0 ppm): δ 14.4 (CH_3), 15.8 (CH_3), 20.2 (CH_3), 26.7 (CH_3), 28.6 (CH), 28.8 (CH_2), 30.0 (CH_2), 39.5 (CH_2), 40.3 (CH), 40.4 (CH_2), 40.8 (CH), 42.7 (CH), 44.5 (CH_2), 62.9 (CH_2), 71.3 (CH_2), 72.6 (CH_2), 72.8 (CH_2), 73.4 (CH_2), 74.8 (CH), 78.4 (CH), 79.6 (CH), 80.3 (CH), 81.1 (CH), 82.5 (CH), 82.6 (CH), 85.2 (CH), 85.6 (CH), 87.6 (CH), 127.5 (CH), 127.61 (CH), 127.64 (CH), 127.7 (CH) × 4, 127.9 (CH) × 2, 128.3 (CH) × 4, 128.5 (CH) × 2, 139.2 (C), 139.5 (C), 139.6 (C); IR (film) ν_{max} 3447, 3061, 3029, 2922, 2853, 1496, 1453, 1436, 1375, 1336, 1285, 1274, 1259, 1071, 1028, 734, 697, 677; LR-FDMS, *m*/*z* 743 ([M$^+$], bp); HR-FDMS, calcd for $C_{46}H_{62}O_8$ [M$^+$]: 742.4445, found: 742.4453.