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Convergent synthesis of the ABCDE-ring part of ciguatoxin CTX3C

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Abstract—Convergent synthesis of the ABCDE-ring part (**2**) of ciguatoxin CTX3C (**1**) has been achieved. A carbanion stabilized by a dimethyldithioacetal *S*-oxide group in the AB-ring part (**4**) readily reacted with an aldehyde group in the E-ring part (**5**). The resulting adduct was facilely converted to the corresponding β,γ-unsaturated α,ε-dihydroxy ketone (**3**). The subsequent reductive hydroxy-ketone-cyclization reactions constructed the CD-ring part efficiently. Thus, the ABCDE-ring part (**2**) was concisely synthesized in 10 steps in 11% overall yield from the AB-ring and the E-ring parts (**4** and **5**).

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][1] by strong binding to voltage-sensitive sodium channels.[3] Its unique ladder-shaped *trans*-fused polycyclic structure possessing 13 ether rings is a synthetic challenge and has attracted the attention of synthetic chemists.[4,5] During the course of our studies directed toward CTXs,[6] we achieved the syntheses of their individual medium ring parts[6h] and developed a convergent method for the construction of their X/6/7/X ring systems.[6g] Here, efficient convergent synthesis of the ABCDE-ring part (**2**)[7] of **1** based on our established methodology is described.

We planned to synthesize the ABCDE-ring part **2** from two parts, AB-ring **4** and E-ring **5** (Scheme 1).[6i] 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 converted to the corresponding β,γ-unsaturated α,ε-dihydroxy ketone **3**. The subsequent reductive hydroxy-ketone cyclization reactions[9] would construct the CD-ring part. We designed the synthesis of **4** from D-glucose derivative **6** through A-ring formation by ring-closing olefin metathesis reaction (RCM). The E ring **5** was planned to be synthesized according to our previous method.[6h] The medium ring part would be constructed by RCM of the corresponding diene precursor **7** derived from the tri-*O*-acetyl D-glucal via C-glycoside **8**.

The synthesis of **4**, started from known D-glucose derivative **6**,[10] is shown in Scheme 2. The diol **6** was converted to 1,1,3,3-tetraisopropyldisiloxan-1,3-diyl (TIPDS) derivative **9** (95% yield). Selective deprotection of the allyl group in **9** using Ogasawara's method[11] followed by Swern oxidation[12] and addition of an allyl Grignard reagent to the resulting lactone produced hemiacetal **10** (87% overall yield), which was treated with EtSH in the presence of $BF_3{\cdot}OEt_2$ to afford diol **11** (80% yield). Conversion of **11** to diol **12** was performed through a three-step process [(i) oxidation of the ethylthio group of **11** followed by one-pot reductive etherification; (ii) formation of a 2-naphthylmethylidene acetal; and (iii) removal of the TIPDS group] (66% overall yield). Diol **12** was selectively protected by TBS and the resultant alcohol was transformed into allyl ether **13**, which was converted to **15** through RCM using Grubbs' first-generation ruthenium catalyst[13] followed by deprotection of the TBS group (40% overall yield from **12**). After protection of **15** as a *p*-bromobenzyl (PBB) ether,

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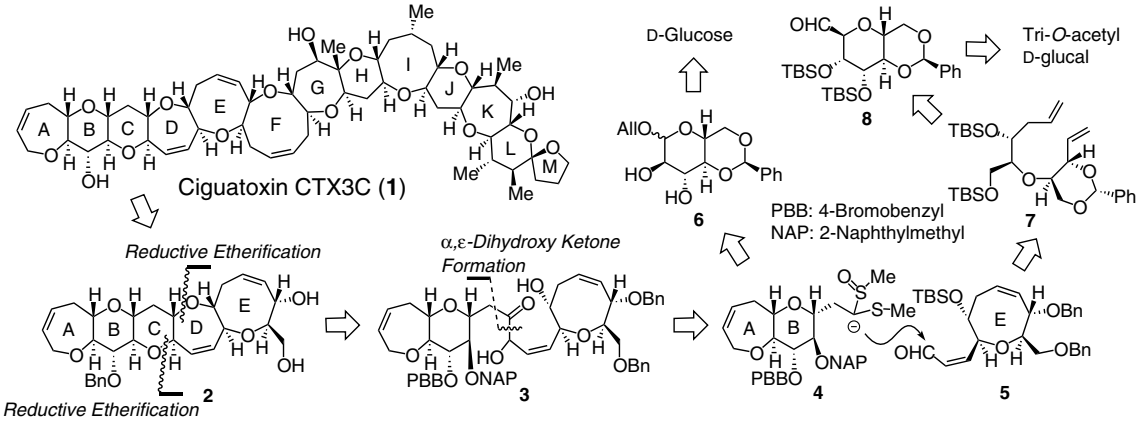
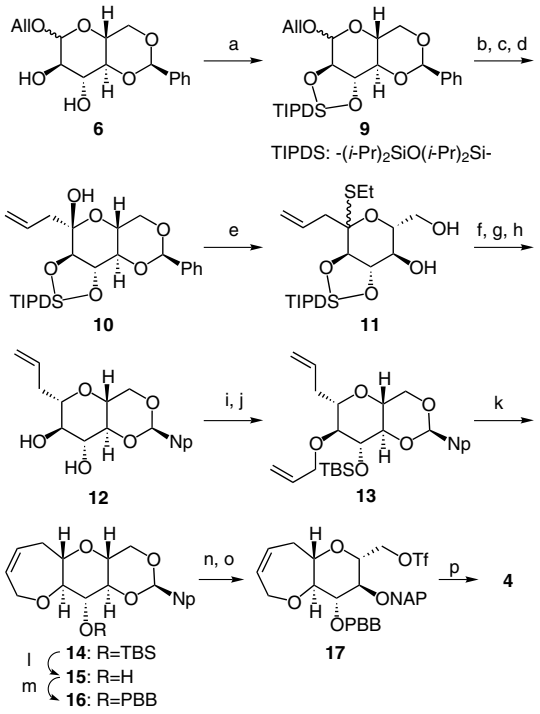


Scheme 1. Synthetic plan for the ABCDE-ring part (**2**) of CTX3C (**1**).

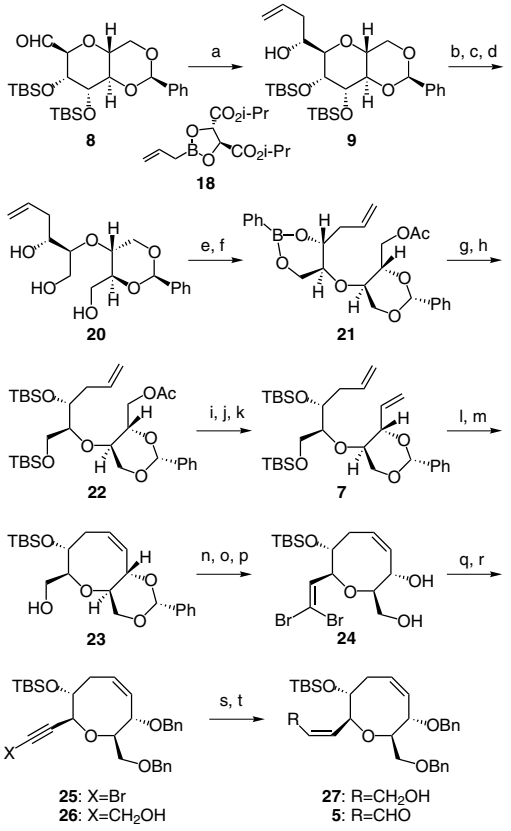


Scheme 2. Synthesis of the AB-ring part **4**. Reagents and conditions: (a) $Cl(i\text{-}Pr)_2SiO(i\text{-}Pr)_2SiCl$, imidazole, DMF, 23 °C, 95%; (b) Et_3Al, $[NiCl_2(dppp)]$ (cat.), toluene, 0 → 24 °C, 99%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 → 0 °C; (d) allylmagnesium bromide, Et_2O, −78 °C, 88% from **9**; (e) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, 80%; (f) *m*CPBA, CH_2Cl_2, 0 °C, then Et_3SiH, $BF_3{\cdot}OEt_2$, 0 °C, 80%; (g) 2-naphthaldehyde, PPTS, benzene, reflux, 92%; (h) TBAF, THF, 23 °C, 90%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (j) allyl bromide, NaH, Bu_4NI, THF, 0 °C; (k) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (cat.), CH_2Cl_2, reflux; (l) TBAF, THF, 23 °C, 40% from **12**; (m) 4-bromobenzyl bromide, NaH, Bu_4NI, THF, 24 °C; (n) $LiAlH_4$, $AlCl_3$, CH_2Cl_2–Et_2O, 24 °C; (o) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (p) $MeSCH_2S(O)Me$, BuLi, THF, −20 °C, then **17**, −20 → 0 °C, 59% from **15**.

reductive cleavage of the naphthylidene acetal **16** and the subsequent formation of a triflate ester gave **17**. The triflate was substituted by lithiated methylthiomethyl methyl sulfoxide to produce **4** (59% overall yield from **15**). Thus, the AB-ring part **4** was synthesized from **6** in 16 steps in 12% overall yield.

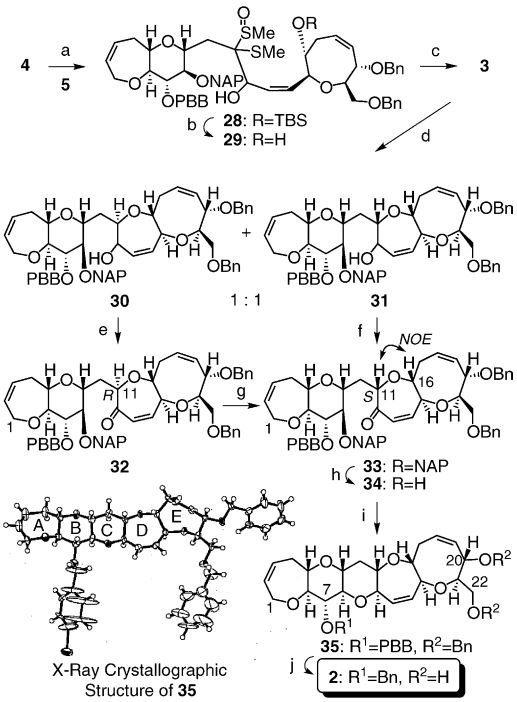
The E-ring part **5** was synthesized from the previously reported aldehyde **8**,[6h] prepared from tri-*O*-acetyl D-glucal in six steps in 49% overall yield (Scheme 3). Allylation of **8** by chiral allylboron reagent **18**[14] gave homoallyl alcohol **19** as the sole product (93% yield). Removal of the TBS groups of **19** followed by oxidative cleavage of the resulting 1,2-diol and the subsequent reduction gave triol **20** (96% overall yield). The triol **20** was selectively protected with phenyl boronic acid and acetic anhydride to afford **21**, which was transformed into bis-TBS ether **22** through a deprotection/protection sequence (64% overall yield from **20**). The bis-TBS ether **22** was converted to diene **7** by a three-step process [(i) removal of the acetyl group; (ii) Swern oxidation;[12] and (iii) Wittig reaction]. Cyclization of **7** using Grubbs' second-generation ruthenium catalyst[15] followed by selective partial removal of the TBS group gave **23** (∼100% overall yield). The alcohol **23** was oxidized to the corresponding aldehyde, which was converted to **24** through dibromoolefination followed by removal of the benzylidene acetal group (88% overall yield). When the diol **24** was protected with benzyl bromide under the basic conditions, dehydrobromination took place synchronously and bromoacetylene **25** was obtained in good yield (100%). The bromoacetylene **25** was transformed into **5** through hydroxymethylation, Lindlar hydrogenation and Dess–Martin oxidation[16] reactions (88% overall yield). Thus, the E-ring part **5** was prepared from the known **8** in 20 steps in 38% overall yield.

Convergent construction of the CD-ring part is illustrated in Scheme 4. Deprotonation of **4** with NaHMDS followed by the reaction with **5** (0.32 equiv) gave **28** in 54% yield based on **5** along with recovered **4** (62% recovery). The adduct **28** was transformed into α,ε-dihydroxy-β,γ-unsaturated ketone **3** through removal of the TBS group with TBAF followed by treatment with TFA in aqueous THF (50% overall yield). The ketone **3** was stable enough to be purified by silica gel flash chromatography. Cyclization of **3** was performed with an excess amount of Et_3SiH in the presence of TMSOTf in CH_2Cl_2 to produce two tetracyclic ethers **30** (47% yield) and **31** (47% yield), which were separately oxidized with DMPI to give **32** (∼100% yield) and **33**



Scheme 3. Synthesis of the E-ring part **5**. Reagents and conditions: (a) **18**, CH_2Cl_2, −78 °C, 93%; (b) TBAF, THF, 23 °C; (c) $NaIO_4$, 1,4-dioxane-H_2O, 23 °C; (d) $NaBH_4$, MeOH, 0 → 23 °C, 96% from **19**; (e) $PhB(OH)_2$, benzene, reduced pressure; (f) Ac_2O, DMAP (cat.), pyridine, 24 °C; (g) H_2O_2, EtOAc, 24 °C; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 24 °C, 64% from **20**; (i) DIBAH, CH_2Cl_2, −78 °C; (j) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 → −20 °C; (k) Ph_3PCH_3Br, NHMDS, THF, −78 → 23 °C, 85% from **22**; (l) [{CH_2(Mes)N}$_2$C] (Cy_3P)(Cl)$_2$Ru=CHPh (cat.), CH_2Cl_2, reflux, ∼100%; (m) AcOH–THF–H_2O (3:1:1), 23 °C, ∼100%; (n) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 → −20 °C; (o) Ph_3P, CBr_4, CH_2Cl_2, 0 °C, 98% from **23**; (p) ethanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C, 90%; (q) BnBr, NaH, Bu_4NI, THF, 24 °C, ∼100%; (r) MeLi, THF, −20 °C, then $(CH_2O)_n$, 0 °C, 93%; (s) H_2, Lindlar cat., EtOH–quinoline (250:1), 95%; (t) DMPI, $NaHCO_3$, CH_2Cl_2, 23 °C, ∼100%.

(81% yield), respectively. The presence of NOE between H11 and H16 in **33** showed that **33** had the desired stereochemistry. The undesired **32** was isomerized into **33** by treatment with DBU in toluene at 90 °C according to the Hirama and co-workers procedure.[17] Selective removal of the NAP group in **33** with DDQ gave **34** (81% yield), which was efficiently cyclized with Et_3SiH–TMSOTf reagent system into pentacyclic ether **35** (93% yield). At this stage, the pentacyclic structure of **35** was confirmed by X-ray crystallographic analysis.[18] Treatment of **35** with an excess amount of lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) induced not only benzyl detachment from oxygenes at C20 and C22 but also conversion of the PBBO group at C7 to a BnO group to produce **2** successfully (78% yield).[19] Thus, concise convergent construction of the ABCDE-ring part **2** of CTX3C from the AB-ring part **4** and E-ring part **5** was achieved in ten steps, including an isomerization step, in 11% overall yield based on **5**.



Scheme 4. Synthesis of the ABCDE-ring part **2**. Reagents and conditions: (a) NaHMDS (0.97 equiv), THF, −78 °C, then **5** (0.32 equiv), **28**: 54% from **5**, recovered **4**: 62%; (b) TBAF, THF, 23 °C, 93%; (c) THF–H_2O–TFA (10:10:1), 23 °C, 54%; (d) TMSOTf (2 equiv), Et_3SiH–CH_2Cl_2 (1:2), 0 °C, **30**: 47%, **31**: 47%; (e) DMPI, CH_2Cl_2, 23 °C, ∼100%; (f) DMPI, CH_2Cl_2, 23 °C, 81%; (g) DBU, toluene, 90 °C, **32**: 33%, **33**: 67%; (h) DDQ, CH_2Cl_2–pH 7 phosphate buffer (10:1), 0 °C, 81%; (i) TMSOTf (2 equiv), Et_3SiH–CH_2Cl_2 (1:4), 0 °C, 93%; (j) LDBB (excess), THF, −78 °C, 78%.

In conclusion, convergent synthesis of the ABCDE-ring part (**2**) of ciguatoxin CTX3C has been achieved from the AB-ring **4** and the E-ring **5**. A carbanion derived from **4** readily reacted with the aldehyde group of **5**. The resulting adduct **28** was facilely converted to the corresponding β,γ-unsaturated α,ε-dihydroxy ketone **3**. The subsequent reductive hydroxy-ketone-cyclization reactions constructed the CD-ring part efficiently. Further studies toward total synthesis of ciguatoxin CTX3C are currently under way in our laboratory.

Crystallographic data (excluding structure factors) of **35** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 243276. 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].

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18. Crystal data of **35**: $C_{43}H_{47}BrO_8$, M 771.74, orthorhombic $P2_12_12_1$ (No. 19), $a = 4.912(2)$ Å, $b = 18.371(6)$ Å, $c = 49.95(1)$ Å, $V = 3695(2)$ Å^3, D_c ($Z = 4$) = 1.387 g/cm^3, $T = 153$ K, $\mu = 11.70$ cm^{-1}. The final R value is 0.060 for 2596 independent reflections with $I > 3\sigma I$ and 470 parameters.
19. Under the conditions, the PBB group at C7-oxygen of **35** was not removed but effectively converted to a Bn group. It could be explained as follows: The PBB group was first reduced by LDBB into an electron-rich *p*-lithiobenzyl group, which was not further affected by LDBB; Then, reductive cleavage of the Bn ether parts at C20 and C22 took place; Finally, protonation of the *p*-lithiobenzyl group during workup produced the benzyl group at C7-oxygen. The details will be described elsewhere.