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Convergent synthesis of the ABCDE ring framework of ciguatoxin

Kenji Maeda, Tohru Oishi, Hiroki Oguri and Masahiro Hirama*

Department of Chemistry, Graduate School of Science, Tohoku University, and CREST, Japan Science and Technology Corporation (JST), Sendai 980-8578, Japan. E-mail: hirama@ykbsc.chem.tohoku.ac.jp

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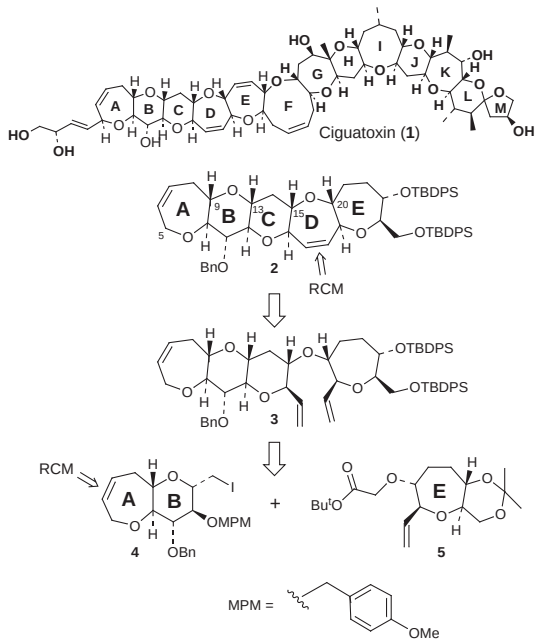
An alkylation–metathesis sequence is shown to be a powerful method to synthesize the ABCDE ring framework of ciguatoxin 1.

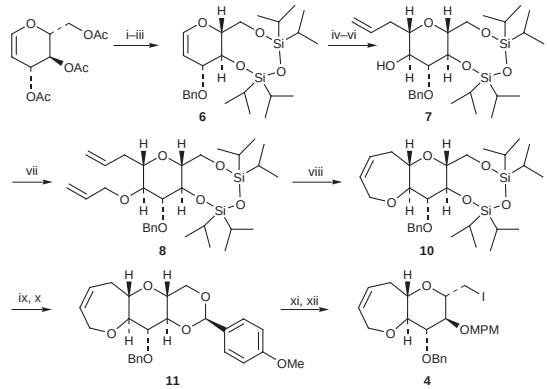
Ciguatoxin (CTX1B, **1**) is the principal toxin that causes ciguatera poisoning.[1] Its gigantic structure and unique agonist activity against the sodium channel have attracted considerable attention among synthetic organic chemists.[2] During the course of our synthetic studies directed toward **1**, we developed an efficient method of constructing *trans*-fused 6,*n*,6,6-tetracyclic ether systems (*n* = 7–10) by combining intermolecular alkylation and ring-closing metathesis (RCM) reactions.[3] We describe herein a convergent synthesis of the ABCDE ring framework **2** of **1** starting from the AB ring **4** and E-ring fragments **5**, using the described alkylation–metathesis strategy (Scheme 1).



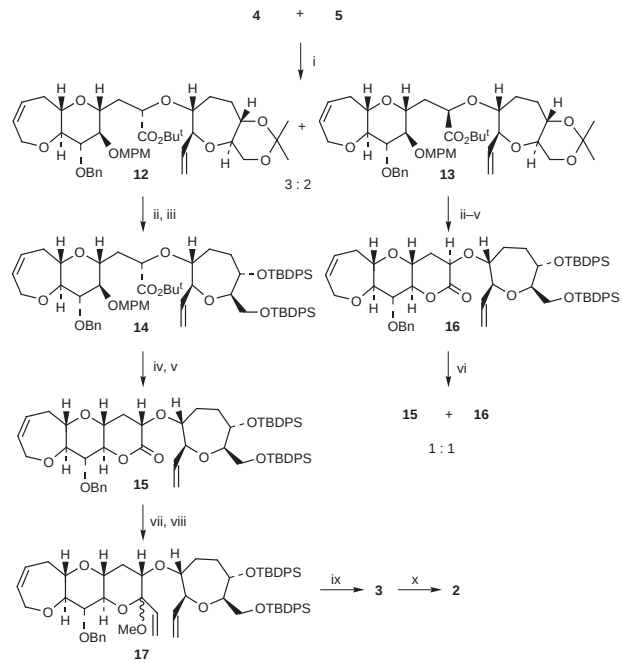
Scheme 1

The synthesis of the iodide **4** is shown in Scheme 2. Tri-*O*-acetyl-D-glucal was converted to **6** *via* methanolysis of the acetate and successive protection of the resulting triol as the tetraisopropyldisiloxanediyl (TIPDS) and benzyl ether. Epoxidation of **6** using Spilling's method[4] followed by addition of CH_2=$CHCH_2MgBr$ resulted in the formation of **7** in 53% overall yield. Allylation of the secondary alcohol of **7** gave **8**, which was subjected to RCM reaction using Grubbs' catalyst, $(PCy_3)_2Cl_2Ru$=CHPh **9**[5] to afford the 7,6-bicyclic system **10** in 94% yield.[6] The TIPDS group of **10** was removed using TBAF and the 1,3-diol was converted to the *p*-methoxybenzylidene acetal **11**. Reductive cleavage of the benzylidene acetal with DIBAL-H followed by conversion of the resulting primary alcohol to an iodide gave **4** regioselectively.[7]

Alkylation of the *tert*-butyl ester **5**, which was readily prepared from D-glucose[8] with **4** using LDA in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) gave a separable mixture of the desired diastereomer **12** and the epimer **13** in a 3 : 2 ratio in 58% combined yield (Scheme 3). When HMPA was used instead of DMPU in this alkylation



Scheme 2 *Reagents and conditions*: i, K_2CO_3 (cat.), MeOH; ii, $(TIPDS)Cl_2$, pyridine; iii, BnBr, NaH, DMF, THF, 0 °C to room temp., 63% (3 steps); iv, NBS, THF–H_2O (9 : 1); v, KHMDS, 18-crown-6, toluene, −75 to 0 °C, 4 h; vi, H_2C=$CHCH_2MgBr$, 0 °C to room temp., 53% (3 steps); vii, H_2C=$CHCH_2Br$, NaH, 0 °C to room temp., 93%; viii, **9** (cat.), CH_2Cl_2, 94%; ix, TBAF, THF; x, PPTS (cat.), *p*-$MeOC_6H_4CH(OMe)_2$, $(CH_2Cl)_2$; xi, DIBAL-H, CH_2Cl_2, −78 to −20 °C, 75% (3 steps); xii, I_2, PPh_3, imidazole, toluene, 82%.



Scheme 3 *Reagents and conditions*: i, LDA, DMPU, THF, −78 to 0 °C, 58% (based on recovery of **4**; 23%); ii, PPTS (cat.), MeOH; iii, TBDPSCl, imidazole, DMF, 71% (2 steps); iv, DDQ, $(CH_2Cl)_2$–H_2O (20 : 1), 91%; v, CSA (cat.), toluene, 80 °C, 80%; vi, imidazole, toluene, reflux, 80% (**15** : **16** = 1 : 1); vii, H_2C=$CHMgBr$, Et_2O, −78 to −60 °C, 91%; viii, CSA (cat.), $HC(OMe)_3$, CH_2Cl_2, 75%; ix, $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, −45 °C, 96%; x, **9**, CH_2Cl_2, 40 °C, 93%.

reaction, the ratio became 1 : 1. Although further attempts to improve the diastereoselectivity and to epimerize **13** were unsuccessful at this stage, we found that the epimerization could be obtained at a later stage (*vide infra*). Acidic methanolysis of the acetonide **12** followed by protection of the resulting 1,3-diol as TBDPS ethers gave **14**. Removal of the *p*-methoxybenzyl group using DDQ followed by treatment with CSA in toluene at 80 °C gave the δ-lactone **15**. The epimeric lactone **16** was also synthesized from **13** in an analogous manner. This lactone was found to undergo epimerization by treatment with imidazole in toluene under reflux to give a separable 1 : 1 mixture of **15** and **16** in 80% yield, while stronger bases such as Bu^{t}OK and DBU caused only decomposition. Thus, the undesired epimer **13** was successfully converted into **15**. Treatment of the lactone **15** with CH_2=CHMgBr followed by conversion of the resultant hemiacetal to the corresponding methyl acetal afforded **17** as a 1 : 1 mixture of anomers. Reduction of the anomeric mixture **17**[9] with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$[10] gave **3** as a single isomer in 96% yield. Finally RCM reaction of **3** with Grubbs' catalyst **9** at 40 °C in CH_2Cl_2 gave the ABCDE ring **2** in 93% yield.[11]

In conclusion, we have demonstrated that the alkylation–metathesis strategy is versatile for the convergent synthesis of the pentacyclic segment **2** of **1**. Further studies directed toward the total synthesis of **1** are currently in progress in our laboratory.

Notes and references

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9 We found that reduction of the ketal rather than the corresponding hemiacetal using Et_3SiH and $BF_3{\cdot}OEt_2$ gave a remarkably higher yield of the reduction product; 0–70% yield in the case of hemiacetal under the same reduction conditions. Also see ref. 3.

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11 The stereochemistry of **2** was unambiguously determined by ^{1}H NMR analysis. *Selected data* for **2**: δ_H (500 MHz, $CDCl_3$) 0.98 (9H, s, TBDPS), 0.99 (9H, s, TBDPS), 1.55 (1H, q, *J* 11.4, H14$_{ax}$), 1.53–1.60 (1H, m, H22), 1.62–1.69 (1H, m, H22′), 1.71–1.78 (1H, m, H21), 2.05–2.14 (1H, m, H21′), 2.29 (1H, dt, *J* 11.4, 4.1, H14$_{eq}$), 2.31-2.38 (1H, m, H8), 2.64 (1H, ddd, *J* 16.0, 7.7, 3.5, H8′), 3.08–3.15 (2H, m, H12, H13), 3.28(0) (1H, ddd, *J* 8.4, 7.7, 3.8, H9), 3.28(5) (1H, ddd, *J* 11.4, 8.9, 4.1, H15), 3.31–3.40 (2H, m, H20, H24), 3.35 (1H, dd, *J* 9.0, 8.4, H10), 3.48 (1H, t, *J* 9.0, H11), 3.62–3.70 (3H, m, H23, H25, H25′), 3.88 (1H, dq, *J* 8.9, 2.3, H16), 4.01 (1H, dq, *J* 16.0, 2.8, H5), 4.12 (1H, dq, *J* 9.0, 2.3, H19), 4.29 (1H, dd, *J* 16.0, 5.7, H5′), 4.83 (1H, d, *J* 11.5, C*H*$_2$Ph), 4.89 (1H, d, *J* 11.5, C*H*$_2$Ph), 5.64 (1H, dt, *J* 13.0, 2.3, H18), 5.77 (1H, dddd, *J* 11.8, 5.1, 3.5, 2.8, H7), 5.83 (1H, dt, *J* 13.0, 2.3, H17), 5.87 (1H, ddt, *J* 11.8, 5.7, 2.8, H6), 7.23–7.43 (17H, m, Ph), 7.52–7.56 (4H, m, Ph), 7.59–7.66 (4H, m, Ph).

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