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Convergent synthesis of the ABCDE ring fragment of ciguatoxins

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Abstract—Synthesis of the ABCDE ring fragment of ciguatoxins has been achieved in a highly stereocontrolled and convergent manner via the *B*-alkyl Suzuki–Miyaura coupling-based approach.

Ciguatera is a seafood poisoning prevalent in tropical and subtropical areas with more than 20,000 victims annually and continues to be a serious public health problem.[1] The principal causative agents, ciguatoxin (**1**)[2] and its congeners including CTX3C (**2**)[3] and 51-hydroxyCTX3C (**3**),[4] are extremely potent neurotoxins that strongly bind to voltage-sensitive sodium channels and inhibit depolarization to allow inward Na^+ influx to continue (Fig. 1).[5] Given the highly complex molecular architecture, extremely potent biological activity, and scarcity in natural sources, ciguatoxins are intriguing target molecules for synthetic chemists. Thus, substantial efforts toward the total synthesis of ciguatoxins have been recorded to date,[6,7] culminating in the first total synthesis of CTX3C by Hirama and co-workers.[8] As part of our synthetic studies on marine polycyclic

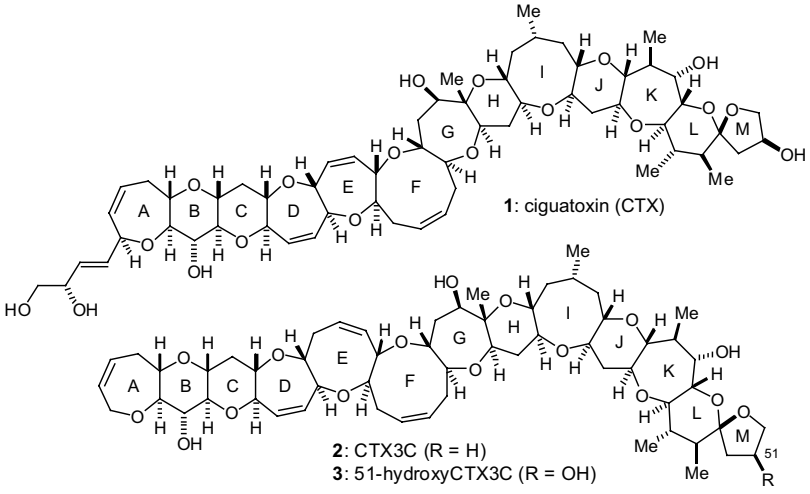

Figure 1. Structures of ciguatoxin (**1**) and its congeners [CTX3C (**2**) and 51-hydroxyCTX3C (**3**)].

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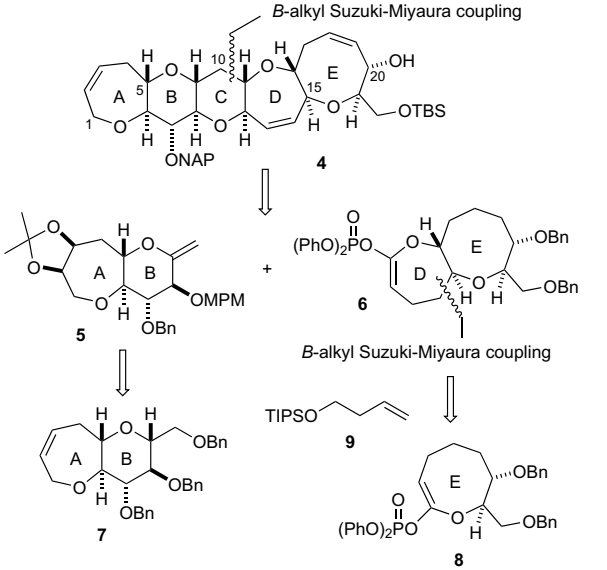
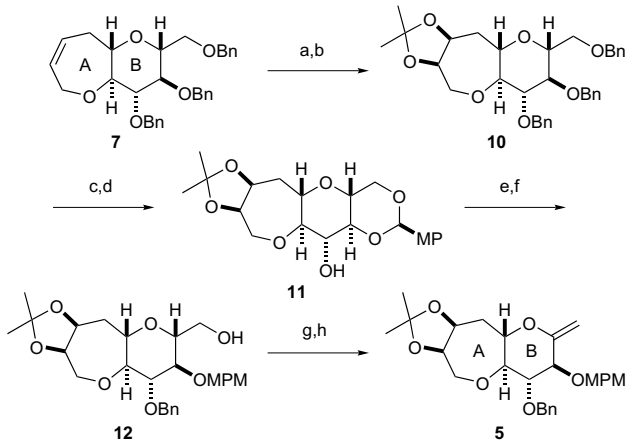
ether toxins,[9] we have developed a powerful method for the convergent synthesis of polycyclic ether arrays based on the *B*-alkyl Suzuki–Miyaura coupling[10,11] and already reported the synthesis of the ABCD ring fragment of ciguatoxins.[12] In this letter, we describe a synthetic route to the ABCDE ring fragment **4** of ciguatoxins with more convergency by extensive use of the *B*-alkyl Suzuki–Miyaura coupling reaction.

Our synthetic planning is briefly given in Scheme 1. We envisaged that the ABCDE ring fragment **4** could be elaborated by the convergent union of the AB ring exocyclic enol ether **5** and DE ring ketene acetal phosphate **6** based on our *B*-alkyl Suzuki–Miyaura coupling-based approach. The AB ring segment **5** should be prepared from the known bicyclic compound **7**.[7h] On the other hand, the DE ring segment **6** could be traced back to the E ring ketene acetal phosphate **8** and olefin **9**, which was planned to be connected by the *B*-alkyl Suzuki–Miyaura coupling.

Synthesis of the AB ring fragment **5** is outlined in Scheme 2. In order to apply the *B*-alkyl Suzuki–Miyaura coupling chemistry, the (*Z*)-olefin within **7** needed to be protected from hydroboration. Thus, stereoselective dihydroxylation of **7** with AD mix-β gave *vic*-diol as a mixture of diastereomers (dr = 87:13), which was protected as the acetonide to give **10**. At this stage, the minor diastereomer could be readily separated by flash column chromatography.[13] Removal of the benzyl groups by hydrogenolysis and the ensuing *p*-methoxybenzylidene acetal formation led to alcohol **11** in high overall yield. After protection of the remaining hydroxyl group of **11** as the benzyl ether (92% yield), the *p*-methoxybenzylidene acetal was regioselectively cleaved with DIBAL-H to deliver alcohol **12** in quantitative yield. Iodination of **12** under standard conditions followed by treatment with NaH in DMF furnished the AB ring fragment **5** in high yield.

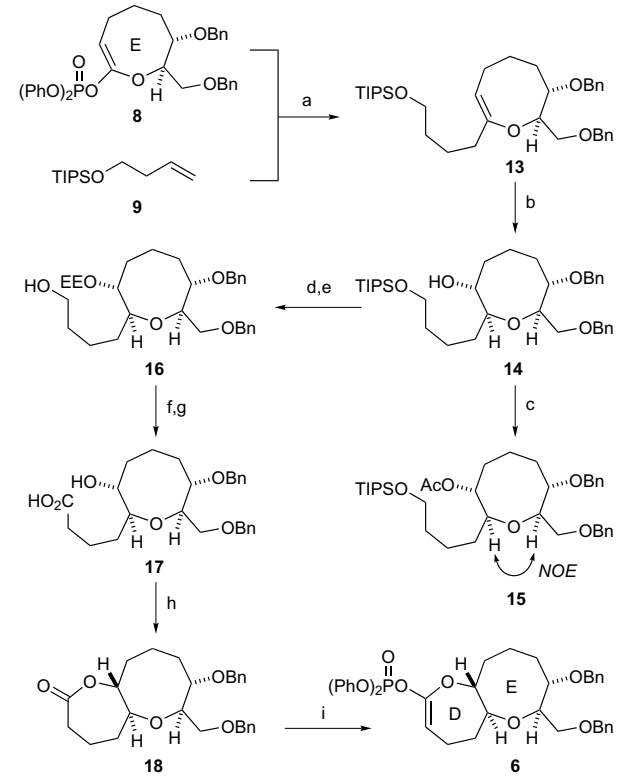


Scheme 1. Synthetic planning of the ABCDE ring fragment **4** of ciguatoxins.



Scheme 2. Synthesis of the AB ring exocyclic enol ether **5**. Reagents and conditions: (a) AD-mix β, $MeSO_2NH_2$, *t*-BuOH/*t*-BuOMe/H_2O, 0 °C; (b) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, quant. (two steps); (c) H_2, Pd/C, EtOAc/MeOH, rt; (d) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, rt, 99% (two steps); (e) BnBr, KO*t*-Bu, *n*-Bu_4NI, THF, rt, 92%; (f) DIBAL-H, CH_2Cl_2, −78 to 0 °C, quant.; (g) I_2, PPh_3, imidazole, THF, rt, 92%; (h) NaH, DMF, 0 °C to rt, 99%.

Synthesis of the DE ring fragment **6** began with the E ring ketene acetal phosphate **8**[12] (Scheme 3). Attachment

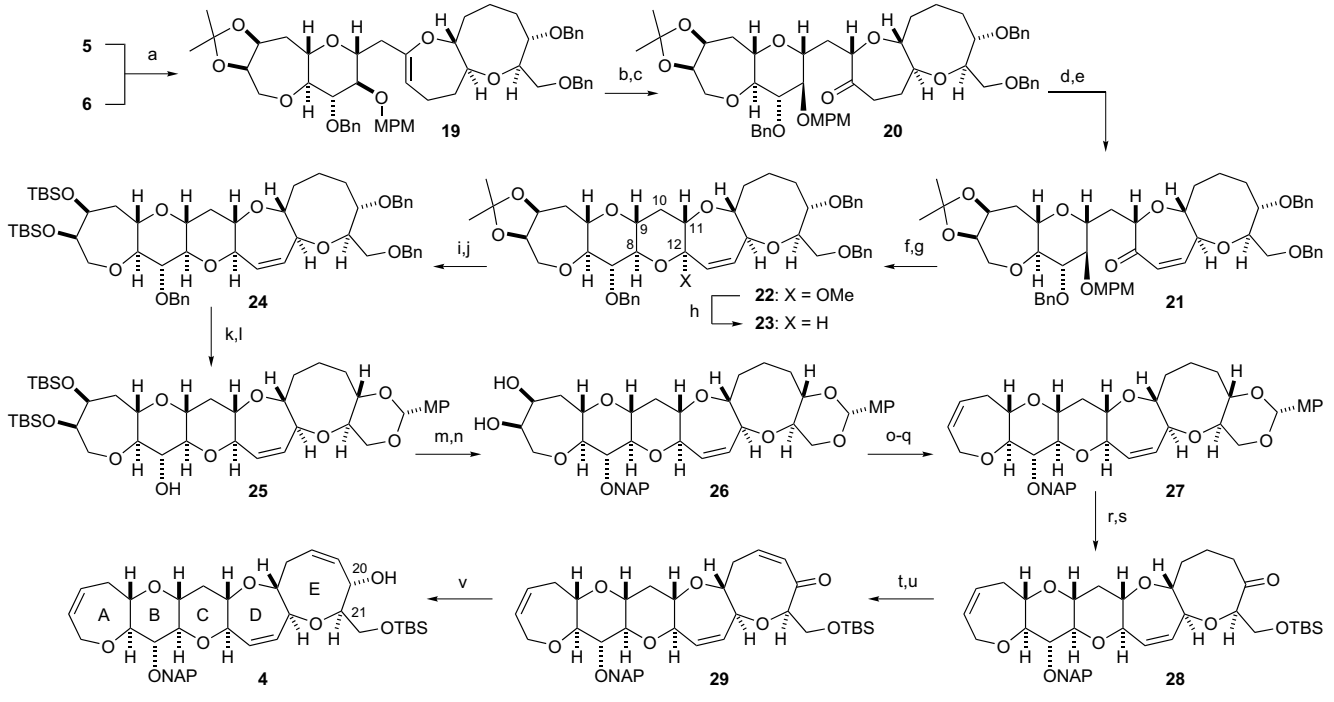


Scheme 3. Synthesis of the DE ring ketene acetal phosphate **6**. Reagents and conditions: (a) 9-BBN, THF, rt; then aq Cs_2CO_3, **8**, $PdCl_2(dppf)\cdot CH_2Cl_2$, DMF, 50 °C, 78%; (b) $ThexylBH_2$, THF, 0 °C; then aq NaOH, 30% H_2O_2, rt, quant.; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 97%; (d) EVE, PPTS, CH_2Cl_2, rt; (e) TBAF, THF, rt; (f) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 0 °C to rt; then aq HCl, rt, 83% (four steps); (h) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt; then DMAP, toluene, 110 °C, 94%; (i) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C.

of the alkyl chain required for constructing the D ring was accomplished via the *B*-alkyl Suzuki–Miyaura coupling. Thus, coupling of **8** with the alkylborane derived from olefin **9** in the presence of aqueous Cs_2CO_3 and 10 mol% of $PdCl_2$(dppf) provided endocyclic enol ether **13** in good yield. Hydroboration of **13** proceeded stereoselectively to yield alcohol **14** in quantitative yield as a single stereoisomer. The stereochemical outcome of the reaction was confirmed by NOE experiment performed on the corresponding acetate **15**. Protection of the resultant alcohol as the ethoxyethyl (EE) ether followed by removal of the silyl group led to alcohol **16**, which was then converted to carboxylic acid **17** by a two-step procedure. Acidic workup of the second oxidation step facilitated deprotection of the EE group. Lactonization of **17** under Yamaguchi conditions afforded lactone **18**, which was then transformed to the DE ring fragment **6** following the Nicolaou protocol.[14]

With the requisite AB and DE ring fragments in hand, we next directed our attention to building up the pentacyclic polyether framework by means of the *B*-alkyl Suzuki–Miyaura coupling-based approach (Scheme 4). To this end, the AB ring exocyclic enol ether **5** was treated with 9-BBN to deliver the corresponding alkylborane, which was in situ reacted with **6** in the presence of aqueous Cs_2CO_3 and $PdCl_2$(dppf) catalyst (10 mol%), giving rise to cross-coupled product **19** in 73% yield from **18**. Hydroboration of **19** with thexylborane followed by oxidation of the resultant hydroxyl group with TPAP/NMO[15] led to ketone **20**. Incorporation of the double bond to the D ring was cleanly performed by conversion to the corresponding enol silyl ether followed by exposure to Pd(OAc)[16] to effect dehydrosilylation, leading to enone **21**. Deprotection of the MPM group of **21** followed by treatment with methyl orthoformate under acidic conditions afforded mixed methyl ketal **22**. Finally, reduction of **22** with Et_3SiH and $BF_3{\cdot}OEt_2$ gave rise to hexacyclic compound **23** as a single stereoisomer. The stereostructure of **23** was unambiguously confirmed by ^1H NMR analysis ($J_{8,9} = 9.2$ Hz, $J_{9,10eq} = 4.2$ Hz, $J_{9,10ax} = 11.4$ Hz, $J_{10eq,11} = 4.2$ Hz, $J_{10ax,11} = 11.4$ Hz, $J_{11,12} = 9.1$ Hz).

Having constructed the pentacyclic polyether skeleton, we set out to functionalize the E ring of **23**. Based on our preliminary experiments, we found that deprotection of the acetonide within **23** required relatively strong acidic conditions. Therefore, the acetonide was removed prior to installing sensitive functionalities. The liberated *vic*-diol was masked with TBSOTf and Et_3N, giving bis-(silyl) ether **24**. The three benzyl groups were then removed by exposure to lithium di-*tert*-butylbiphenylide (LiDBB),[17] and the resultant triol was treated with *p*-methoxybenzylidene dimethylacetal and PPTS to deliver alcohol **25**. Protection of the remaining hydroxyl group as the 2-naphthylmethyl (NAP)[8b] ether (KH, NAPBr) followed by deprotection of the two silyl groups with



Scheme 4. Convergent synthesis of the ABCDE ring fragment **4**. Reagents and conditions: (a) 9-BBN, THF, rt; then aq Cs_2CO_3, **6**, $PdCl_2$(dppf)·CH_2Cl_2, DMF, 50 °C, 73% from **18**; (b) $ThexylBH_2$, THF, 0 °C; then aq NaOH, 30% H_2O_2, rt, 78%; (c) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt; (d) LiHMDS, THF, −78 °C; then TMSCl, Et_3N, −78 °C; (e) $Pd(OAc)_2$, MeCN, rt, 89% (three steps); (f) DDQ, pH 7 buffer/CH_2Cl_2, rt, 85%; (g) $HC(OMe)_3$, PPTS, toluene, 50 °C; (h) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2/MeCN, −15 °C, 73% (two steps); (i) aq HCl, THF/MeOH, 50 °C; (j) TBSOTf, Et_3N, CH_2Cl_2, rt, 98% (two steps); (k) LiDBB, THF, −78 °C; (l) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, rt, 77% (two steps); (m) NAPBr, KH, THF, rt, 96% (based on recovered **25**); (n) TBAF, THF, rt; (o) $HC(OMe)_3$, PPTS, CH_2Cl_2, rt; (p) Ac_2O, reflux, 88% (three steps); (q) CSA, MeOH, 0 °C; (r) TBSCl, imidazole, DMF, 0 °C, 94% (two steps); (s) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt; (t) LiHMDS, TMSCl, Et_3N, THF, −78 °C; (u) $Pd(OAc)_2$, MeCN, rt, 74% (three steps); (v) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_2Cl_2/MeOH, 0 °C, 91%.

TBAF led to diol **26**. *ortho* Ester formation of the resultant diol ($HC(OMe)_3$, PPTS) followed by thermolysis (Ac_2O, reflux)[18] cleanly regenerated the (*Z*)-olefin of the A ring to furnish **27**. Cleavage of the *p*-methoxybenzylidene acetal under mild acidic conditions and selective protection of the primary alcohol as the TBS ether, followed by oxidation of the remaining secondary alcohol, led to ketone **28**, which was then transformed to enone **29** according to the Ito–Saegusa procedure. Finally, reduction of **29** under Luche conditions[19] furnished the targeted ABCDE ring fragment **4** as a single stereoisomer. The stereochemical relationship between 20-H and 21-H was determined to be *anti* based on ^1H NMR analysis ($J_{20,21} = 9.5$ Hz).

In summary, we have succeeded in the synthesis of the ABCDE ring fragment of ciguatoxins via the Suzuki–Miyaura coupling-based approach. The highly stereocontrolled, convergent nature of the present synthesis allowed an efficient and straightforward production of the ABCDE ring fragment. Further efforts toward the total synthesis of ciguatoxins are currently underway and will be reported in due course.

Acknowledgements

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