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Progress toward the Total Synthesis of Ciguatoxins: A Convergent Synthesis of the FGHIJKLM Ring Fragment

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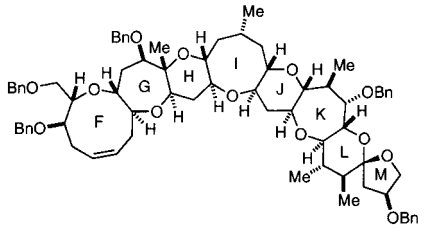
ABSTRACT



A highly convergent synthetic route to the FGHIJKLM ring fragment of ciguatoxins has been developed, which relied on extensive use of the *B*-alkyl Suzuki–Miyaura coupling reaction.

Ciguatera is a seafood poisoning prevalent in subtropical and tropical areas with more than 20 000 victims annually and continues to be a public health hazard.[1,2] The causative toxins originate in an epiphytic dinoflagellate *Gambierdiscus toxicus*[3] and are accumulated in fish through the food chain, thus causing human intoxication. The principal toxins, ciguatoxin (CTX, **1**)[4] and a number of congeners, including CTX3C (**2**)[5] and 51-hydroxyCTX3C (**3**),[6] are extremely potent neurotoxins that bind to voltage-sensitive Na^+-channels (VSSC) and inhibit depolarization to allow inward Na^+ influx to continue.[7] The complex molecular architecture, remarkable biological activity, and natural scarcity of these toxins make them attractive and challenging targets for total synthesis,[8−10]

[†] The University of Tokyo and CREST, JST.
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culminating in the first total synthesis of **2** by Hirama, Oishi, and co-workers.[11] As part of our studies directed toward the total synthesis of ciguatoxins and related compounds, we have engaged in development of a general method for the convergent assembly of a polycyclic ether structure based on the *B*-alkyl Suzuki−Miyaura coupling.[8h,12−14] Herein we describe a highly convergent synthesis of the FGHIJKLM ring fragment **4** of ciguatoxins by extensive use of the *B*-alkyl Suzuki−Miyaura coupling reaction.

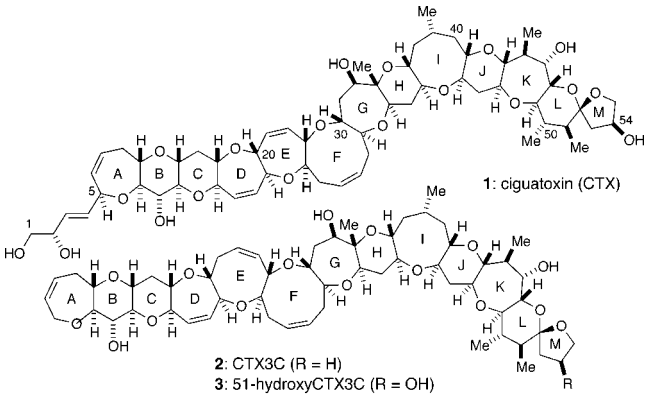
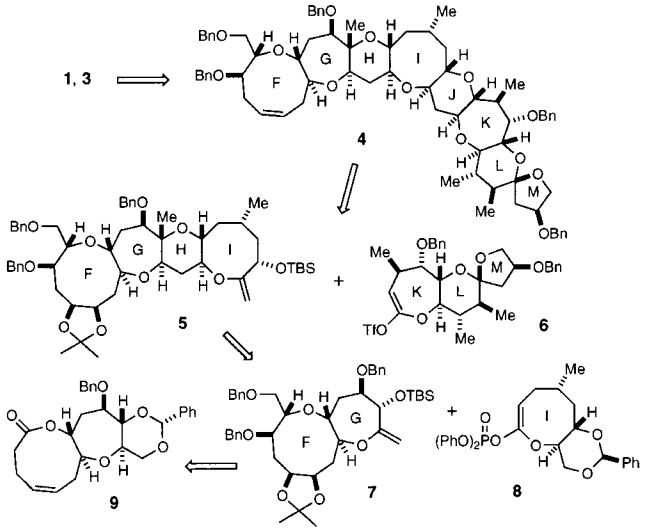


Figure 1. Structures of ciguatoxin (CTX, **1**) and its analogues [CTX3C (**2**) and 51-hydroxyCTX3C (**3**)].

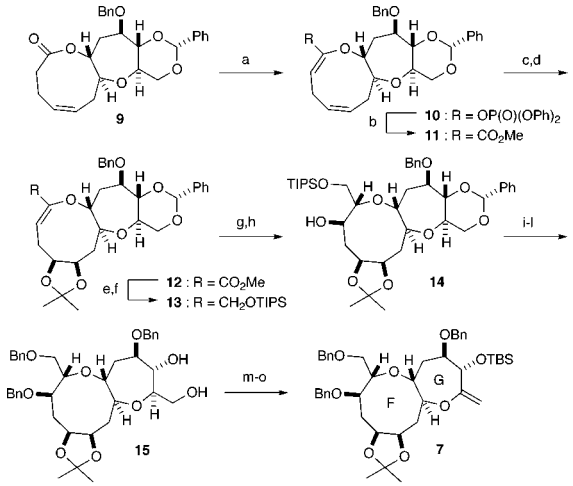
We previously reported approaches to the synthesis of the G−M ring fragment of ciguatoxins.[8h] However, attempts to construct the F ring from this advanced intermediate were fruitless. These results prompted us to explore the synthesis of the octacyclic polyether **4** with more convergency (Scheme 1). The target compound **4** was planned to be assembled by

Scheme 1. Retrosynthetic Analysis of Compound **4**



2-fold *B*-alkyl Suzuki−Miyaura coupling from the FG, I, and KLM ring fragments (**7**, **8**, and **6**, respectively). Moreover, formation of a nine-membered ether ring within

Scheme 2. Synthesis of the FG Ring Exocyclic Enol Ether **7**[a]



[a] Reagents and conditions: (a) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C. (b) $Pd(PPh_3)_4$, CO, MeOH, Et_3N, DMF, 50 °C, 76% (two steps). (c) AD mix-α, $MeSO_2NH_2$, *t*-BuOH/THF/H_2O, 0 °C. (d) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 79% (two steps) (+α-diol acetonide, 18%). (e) DIBALH, CH_2Cl_2, −78 °C. (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt. (g) DMDO, CH_2Cl_2, −20 °C. (h) Et_3SiH, BH_3•THF, CH_2Cl_2, 0 °C, 75% (four steps). (i) TBAF, THF, rt, 97%. (j) KO*t*-Bu, BnBr, THF, rt, 98%. (k) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, then $Me_2C(OMe)_2$, rt, 78% (two steps). (l) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, 86%. (m) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt. (n) CSA, MeOH/CH_2Cl_2, 0 °C, 96% (two steps). (o) I_2, PPh_3, imidazole, THF, rt. (p) KO*t*-Bu, THF, 0 °C, 86% (two steps).

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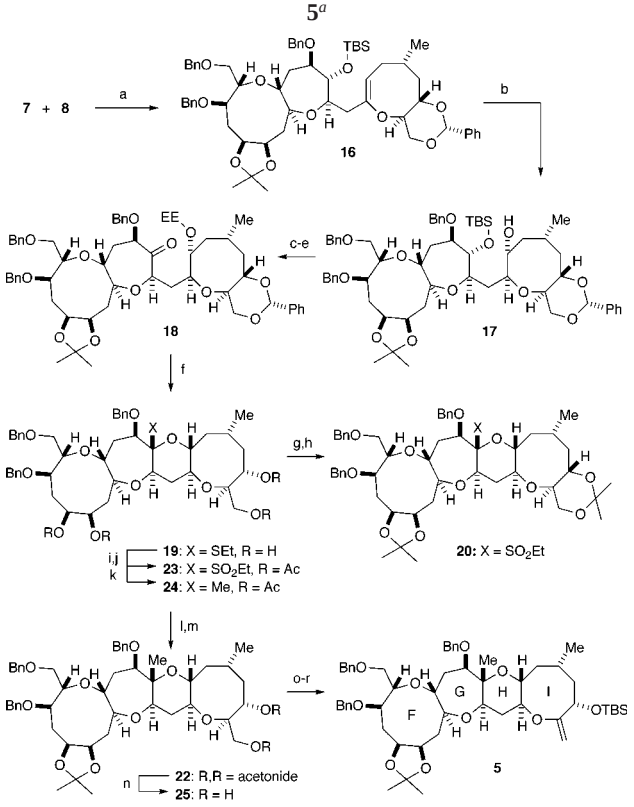
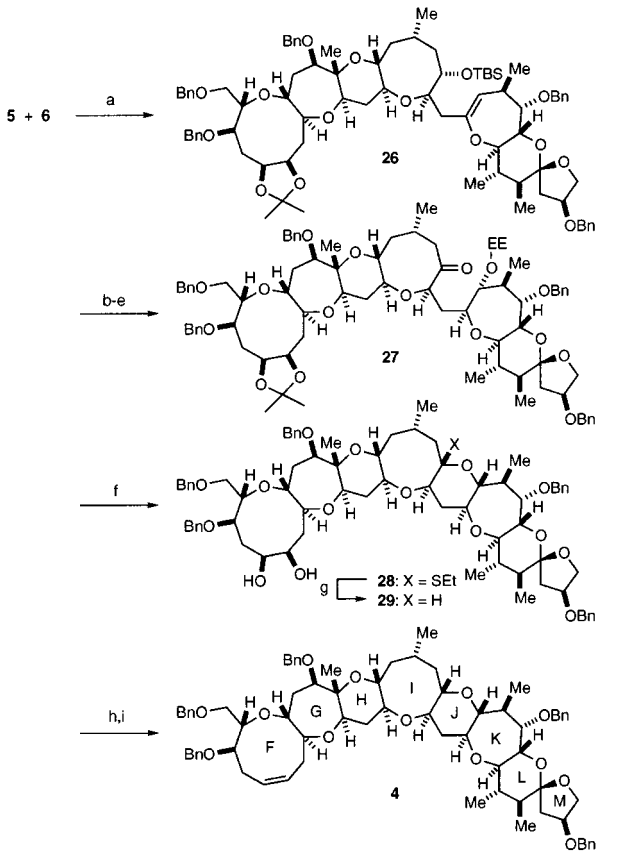
Scheme 3. Synthesis of the FGHI Ring Exocyclic Enol Ether 5[a]



[a] Reagents and conditions: (a) **7**, 9-BBN−H, THF, rt, then 1 M $NaHCO_3$, **8**, $Pd(PPh_3)_4$, DMF, rt, 85%. (b) DMDO, CH_2Cl_2, −20 °C, then Et_3SiH, BH_3·THF, CH_2Cl_2, −20 °C, 82% (two steps). (c) EVE, CSA, CH_2Cl_2, rt. (d) TBAF, THF, rt, 94% (two steps). (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 96%. (f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt. (g) $Me_2C(OMe)_2$, CH_2Cl_2, rt, 68% from **18**. (h) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C. (i) Ac_2O, pyridine, rt. (j) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 84% from **18**. (k) $AlMe_3$, *t*-BuOMe, 0 °C. (l) K_2CO_3, MeOH, 60 °C. (m) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 58% from **23** (+**21**, 38%). (n) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, 89%. (o) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt. (p) CSA, MeOH/CH_2Cl_2, 0 °C, 83% (two steps). (q) I_2, PPh_3, imidazole, THF, rt. (r) KO*t*-Bu, THF, 0 °C, 94% (two steps).

Scheme 4. Synthesis of the FGHIJKLM Ring System **4**[a]



[a] Reagents and conditions: (a) **5**, 9-BBN−H, THF, rt, then 3 M Cs_2CO_3, **6**, $Pd(PPh_3)_4$, DMF, rt, 61%. (b) BH_3·THF, THF, rt, then aq NaOH, H_2O_2, rt, 93%. (c) EVE, CSA, CH_2Cl_2, rt. (d) TBAF, THF, rt, 73% (two steps). (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 92%. (f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, 73%. (g) Ph_3SnH, AIBN, toluene, 110 °C. (h) $HC(OMe)_3$, PPTS, CH_2Cl_2, rt. (i) Ac_2O, 160 °C, 87% (three steps).

7 was envisioned to be constructed from lactone **9** through Pd(0)-mediated carbonylation of lactone-derived enol phosphate.[8f]

Synthesis of the FG ring exocyclic enol ether **7** began with lactone **9**,[15] which was converted to the enol phosphate **10** (Scheme 2).[16] Pd(0)-catalyzed carbonylation[8f] of **10** proceeded smoothly to give enoate **11** in 76% yield over two steps. At this stage, the disubstituted olefin moiety was masked as the protected diol. Dihydroxylation of **11** with AD mix-α proceeded regio- and stereoselectively, and subsequent acetonide formation gave *β*-diol acetonide **12** in 79% yield.[17] DIBALH reduction was followed by protection as its TIPS ether to give **13**, which upon epoxidation with dimethyldioxirane (DMDO) and immediate reduction with Et_3SiH and BH_3·THF[8h] produced **14** as the sole product (75% yield over four steps). Alcohol **14** was then converted to diol **15** by a five-step sequence as shown. Subsequent silylation followed by selective removal of the primary TBS group, iodination of the derived alcohol, and subsequent treatment with a base provided the requisite exocyclic enol ether **7** in good overall yield.

Coupling of the FG and I rings followed by closure of the H ring is summarized in Scheme 3. Hydroboration of **7**

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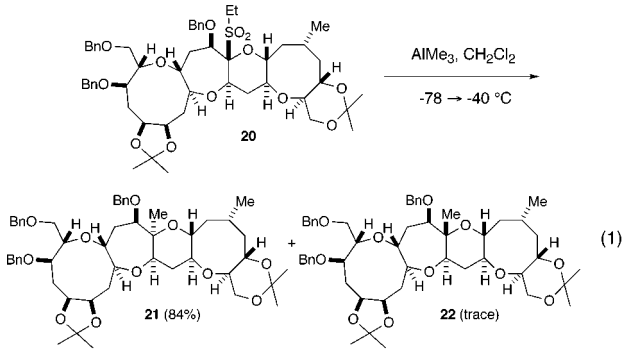
(17) The corresponding α-diol acetonide was formed in 18% yield, which was potentially useful and could be converted to **4**.

with 9-BBN−H and subjection of the resultant alkylborane to enol phosphate **8**[8h] [aqueous 1 M $NaHCO_3$, $Pd(PPh_3)_4$, DMF, room temperature][12] afforded cross-coupled product **16**. Epoxidation of **16** with DMDO in CH_2Cl_2 and subsequent reduction of unstable intermediary epoxide (Et_3SiH, BH_3·THF)[8h] were carried out in one pot to give alcohol **17** in 82% overall yield (three steps). Protection of the alcohol as its ethoxy ethyl (EE) ether followed by desilylation and oxidation of the resultant alcohol provided ketone **18**. Exposure of **18** with EtSH and $Zn(OTf)_2$ effected mixed thioketal formation with concomitant loss of the acetal groups to afford tetraol **19**. Reprotection of **19** as its bis-acetonide and sulfide oxidation gave sulfone **20**. However, treatment of **20** with $AlMe_3$ led to the undesired α-methylated product **21** in 84% yield along with a trace amount of the desired *β*-methylated **22** (eq 1). After extensive experimentation, it was eventually discovered that exposure of tetraacetate **23**, derived from **19**, to $AlMe_3$ in *tert*-butyl methyl ether led to a mixture (ca. 1:1.5) of α- and *β*-methylated products with the latter **24** predominating.[18] The mixture, without separation, was deacetylated and reprotected as the bis-acetonide to afford the desired **22** in 58% yield from **23** along with **21** (38% yield) (Scheme 3). Selective removal of the six-membered acetonide group by using EtSH and $Zn(OTf)_2$ afforded diol **25**, which was readily converted to the FGHI ring fragment **5** (71% overall yield from **25**).

The second Suzuki−Miyaura coupling of an alkylborane derived from **5** with the KLM ring enol triflate **6**[8h] proceeded smoothly to provide coupled product **26** in 61% yield (Scheme 4). Hydroboration−oxidation, alcohol protection,



desilylation, and oxidation with TPAP/NMO[19] gave ketone **27** exclusively (62% overall yield). Exposure of **27** to EtSH and $Zn(OTf)_2$ afforded mixed thioketal **28**, which upon radical reduction[8h,12f,20] provided octacyclic ether **29**. Introduction of the cis double bond into the F ring was performed by ortho ester formation of the *vis*-diol followed by thermolysis in acetic anhydride[21] to furnish the targeted FGHIJKLM ring fragment **4** in 87% yield (three steps).

In conclusion, a highly convergent synthetic route to the FGHIJKLM ring fragment **4** of ciguatoxins has been achieved on the basis of extensive use of the *B*-alkyl Suzuki−Miyaura reaction. Further studies directed toward the total synthesis of ciguatoxins are in progress and will be reported in due course.

Acknowledgment. This work was financially supported in part by a grant from Suntory Institute for Bioorganic Research (SUNBOR).

Supporting Information Available: Synthetic scheme for compound **9** and experimental procedures and spectroscopic data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The effect of protective groups on the ability to generate **24** is not easily understood, but the dioxolane ring attached to the F ring of **20** may interefere with the approach of Me_3Al to the oxocarbenium ion from the *β*-face.

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