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Synthetic Studies on Ciguatoxin: A Highly Convergent Synthesis of the GHIJKLM Ring System Based on *B*-Alkyl Suzuki Coupling

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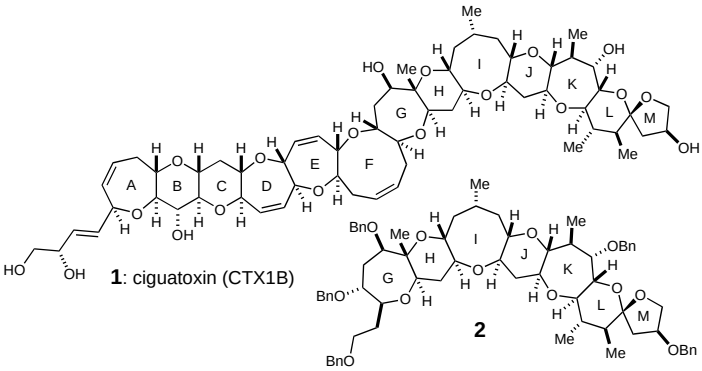
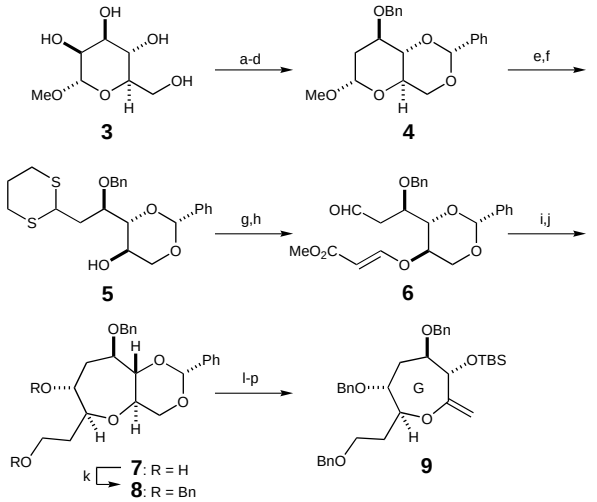
Ciguatoxin (CTX1B, **1**) and its congeners, naturally occurring polycyclic ethers originating from marine unicellular algae, are the principal toxins associated with ciguatera fish poisoning.[1, 2] These potent neurotoxins reportedly bind to the same site of voltage-sensitive sodium channels as brevetoxins, another class of structurally related marine toxins.[3] Their structural complexity and exceptionally potent neurotoxicity, as well as their limited availability from natural sources, have attracted the interest of synthetic chemists, and a number of synthetic studies by us[4] and others[5, 6] have been reported. Recently, we developed a powerful strategy for the convergent assembly of a polyether structure based on *B*-alkyl Suzuki coupling.[7–9] Here we describe the application of this strategy to a more highly functionalized system, which led to a convergent synthesis of the GHIJKLM ring fragment **2** of ciguatoxin.



Synthesis of exo-olefin **9**, corresponding to the G ring, started with methyl α-D-mannopyranoside (**3**), which was converted into **4** by a four-step sequence including benzylidene acetal formation, regioselective tin-mediated benzylation of the equatorial alcohol,[10] and Barton deoxygenation of the remaining hydroxy group[11] (Scheme 1). Compound **4** was treated with 1,3-propanedithiol in the presence of concen-



Scheme 1. Synthesis of the G ring exo-olefin **9**. a) $PhCH(OMe)_2$, CSA, DMF, RT; b) nBu_2SnO, benzene, reflux, then CsF, BnBr, DMF, RT; c) NaH, CS_2, MeI, THF, RT; d) nBu_3SnH, AIBN, benzene, reflux, 24% (4 steps); e) $HS(CH_2)_3SH$, conc. HCl, $CHCl_3$, RT; f) $PhCH(OMe)_2$, CSA, CH_2Cl_2, RT, 46% (2 steps); g) methyl propiolate, NMM, CH_2Cl_2, RT, 97%: h) MeI, $NaHCO_3$, $MeCN/H_2O$, RT, 98%; i) SmI_2, MeOH, THF/HMPA, 0 °C; j) $LiAlH_4$, THF, RT, 72% (2 steps): k) NaH, BnBr, DMF, RT, 84%; l) CSA, MeOH, RT, 89%; m) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT; n) CSA, MeOH, 0 °C, 89% (2 steps); o) I_2, PPh_3, imidazole, THF, RT, p) *t*BuOK, THF, RT, 85% (2 steps). AIBN = 2,2′-azobisisobutyronitrile, Bn = benzyl, CSA = camphorsulfonic acid, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosphoric triamide, NMM = *N*-methylmorpholine, OTf = trifluoromethanesulfonate, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

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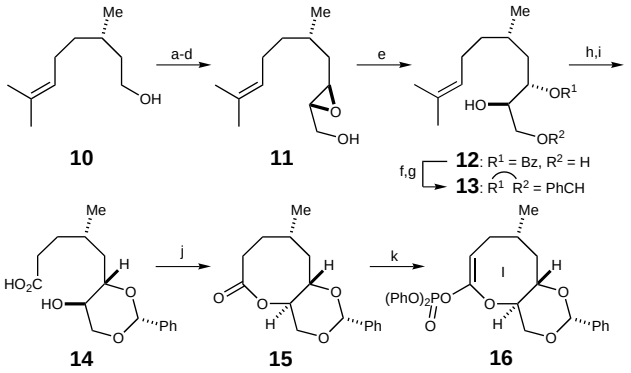
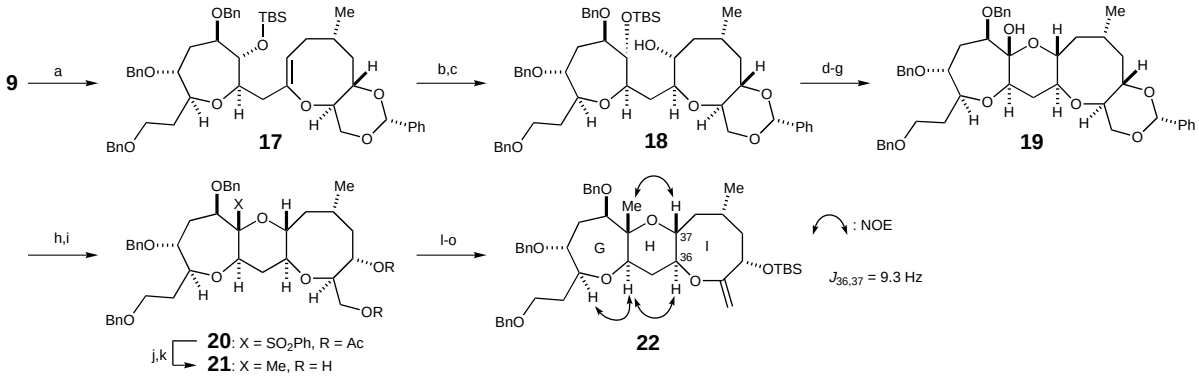
trated HCl, and the resulting dithiane triol was protected as the benzylidene acetal **5**. Alcohol **5** was converted to the corresponding β-alkoxyacrylate, which on treatment with methyl iodide gave aldehyde **6** in 95% yield for the two steps. SmI_2-mediated reductive cyclization[12] of **6** in the presence of HMPA led to stereoselective formation of a seven-membered ether ring. Reduction of the unpurified product thus obtained with $LiAlH_4$ provided diol **7** as a single isomer in 72% yield for the two steps, which was then benzylated to give **8**. Removal of the benzylidene acetal was followed by silylation to give a bis-silyl ether. Selective removal of the primary TBS group followed by iodination of the resulting alcohol and subsequent treatment with a base completed the synthesis of the desired exo-olefin **9** (56% overall yield from **7**).

Construction of enol phosphate **16**, representing the I ring, began with (*S*)-(−)-citronellol (**10**; Scheme 2). Oxidation with $SO_3\cdot$pyridine followed by Wittig reaction gave the homologated α,β-unsaturated ester, which was subjected to DIBALH reduction and subsequent asymmetric epoxidation to afford epoxy alcohol **11** in 79% overall yield. Regioselective opening of the epoxide ring with ammonium benzoate and $Ti(OiPr)_4$[13] gave 1,2-diol **12** in 70% yield as the only isomer detectable by ^1H NMR spectroscopy (500 MHz). Methanolysis of the benzoyl group followed by selective protection of the 1,3-diol as the benzylidene acetal yielded alcohol **13** in 49% yield for the two steps. Oxidative cleavage of the double bond and subsequent oxidation of the resultant aldehyde with sodium chlorite provided hydroxy acid **14** in 66% overall yield. Lactonization of **14** under Yamaguchi conditions[14] gave eight-membered lactone **15** (83%), which was readily converted into enol phosphate **16** by the procedure of Nicolaou et al.[15]



Scheme 2. Synthesis of the I ring enol phosphate **16**. a) $SO_3\cdot$pyridine, Et_3N, CH_2Cl_2, DMSO, 0 °C; b) $Ph_3P{=}CHCO_2Me$, benzene, RT; c) DIBALH, CH_2Cl_2, −78 °C, 86% (3 steps); d) *t*BuOOH, (−)-DET, $Ti(OiPr)_4$, 4-Å molecular sieves, CH_2Cl_2, −20 °C, 92%; e) $PhCO_2NH_4$, $Ti(OiPr)_4$, CH_2Cl_2, RT, then 5% aqueous H_2SO_4, 70%; f) KOH, MeOH, RT, 81%; g) $PhCH(OMe)_2$, CSA, CH_2Cl_2, RT, 61%; h) OsO_4, NMO, acetone/H_2O, RT, then $NaIO_4$, 70%; i) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, RT, 95%; j) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, benzene, reflux, 83%; k) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C, 95%. DMSO = dimethyl sulfoxide, DIBALH = diisobutylaluminum hydride, DET = diethyl tartrate, DMAP = 4-dimethylaminopyridine, KHMDS = potassium hexamethyldisilazide, NMO = *N*-methylmorpholine *N*-oxide.

Hydroboration of **9** with 9-BBN and treatment of the resultant alkylborane with enol phosphate **16** under the previously reported conditions[7b] afforded cross-coupled product **17** in high yield (Scheme 3). Hydroboration of **17** with $BH_3\cdot$THF under various conditions provided the desired alcohol **18** in only low yield, presumably due to the steric hindrance of the methyl group on the eight-membered ring. We eventually solved the problem in the following manner: Epoxidation of **17** with 3,3-dimethyldioxirane[16] proceeded stereoselectively to yield the corresponding α-epoxide, which was immediately reduced with Et_3SiH in the presence of $BH_3\cdot$THF to deliver **18** as the only isolable product in 60% yield for the two steps. Protection of the secondary alcohol as the *p*-methoxybenzyl ether, desilylation followed by oxidation of the resultant alcohol with TPAP/NMO,[17] and oxidative removal of the PMB group with DDQ provided hemiketal **19** as a single stereoisomer. Exposure of **19** to EtSH and $Zn(OTf)_2$ effected formation of the mixed thioketal and removal of the benzylidene group to give a diol. In situ acetylation of the diol was followed by thiol oxidation to yield



Scheme 3. Synthesis of the GHI ring system **22**. a) 9-BBN, THF, RT, then 1M aqueous $NaHCO_3$, **16**, $[Pd(PPh_3)_4]$, DMF, 50 °C, 85% based on **16**; b) DMDO, acetone, −78 → −20 °C; c) Et_3SiH, $BH_3\cdot$THF, CH_2Cl_2, −20 °C, 60% (2 steps); d) *t*BuOK, PMBCl, nBu_4NI, THF, RT, 80%; e) TBAF, THF, RT, 97%; f) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2, RT, quant.; g) DDQ, CH_2Cl_2/pH 7 phosphate buffer (10/1), RT; h) EtSH, $Zn(OTf)_2$, CH_2Cl_2, RT, then Ac_2O, DMAP, Et_3N, 0 °C, 84% (3 steps); i) *m*CPBA, CH_2Cl_2, RT, 96%; j) Me_3Al, CH_2Cl_2, −78 → 0 °C; k) K_2CO_3, MeOH, RT, 83% (2 steps); l) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT; m) CSA, MeOH/CH_2Cl_2 (1/1), 0 °C, 84% (2 steps); n) I_2, PPh_3, imidazole, THF, RT, 94%; o) *t*BuOK, THF, 0 °C, 87%. 9-BBN = 9-borabicyclononane, DDQ = 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone, DMDO = 3,3-dimethyldioxirane, *m*CPBA = *m*-chloroperbenzoic acid, PMB = *p*-methoxybenzyl, TBAF = tetra-*n*-butylammonium fluoride, TPAP = tetrapropylammonium perruthenate.

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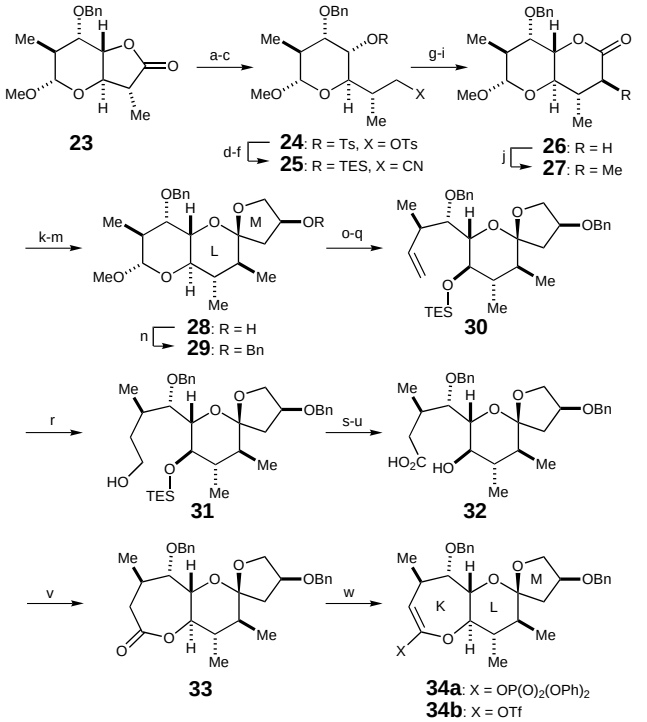
sulfone **20** in 62% overall yield from **18**. Reaction of **20** with Me_3Al[7d, 18] provided the desired methylated compound along with the product of its monodeacetylation at the primary position. Methanolysis of this mixture gave diol **21** in 83% yield for the two steps. Straightforward protecting and functional group manipulations transformed **21** into the requisite exo-olefin **22**. The configuration of **22** was unambiguously determined by the coupling constant $J_{36,37} = 9.3$ Hz and NOE experiments, as shown in Scheme 3.

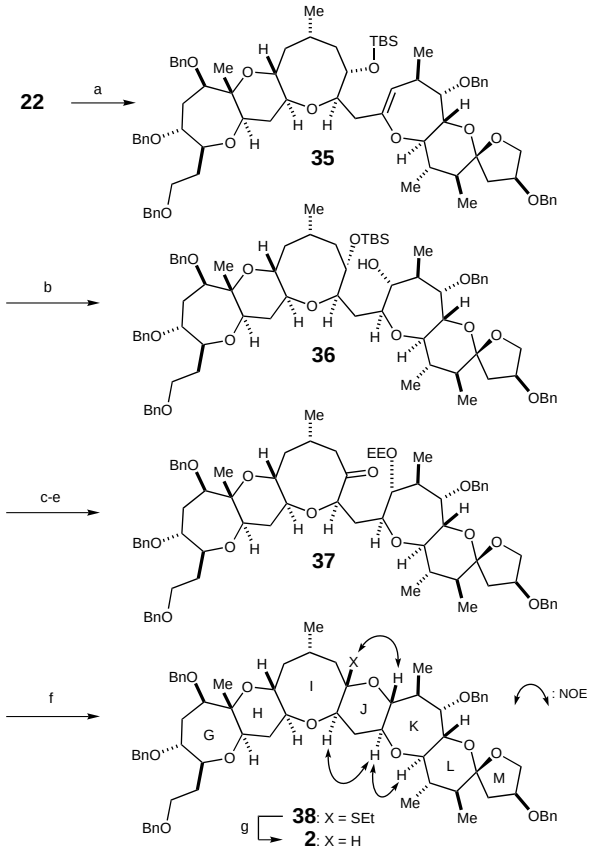
Synthesis of the KLM ring enol phosphate **34a** is summarized in Scheme 4. Bicyclic lactone **23**[4d] was transformed into nitrile **25** via bis-tosylate **24** in a six-step sequence. Reduction of **25** with DIBALH followed by removal of the TES group with acid gave the corresponding hemiacetal, which was then oxidized with TPAP/NMO to give lactone **26** in 78% yield for the three steps. Methylation of the lithium enolate derived from **26** led exclusively to methylated lactone **27** in 82% yield. Construction of the spiroketal M ring was accomplished by asymmetric dihydroxylation with Corey's ligand[19] by following the previously reported method.[4d] Treatment of tricyclic



Scheme 4. Synthesis of the KLM ring system **34**. a) DIBALH, CH_2Cl_2, $-78\,^\circ C$; b) $NaBH_4$, MeOH, $0\,^\circ C$; c) TsCl, Et_3N, DMAP, CH_2Cl_2, RT, 68% (3 steps); d) KCN, DMSO, $70\,^\circ C$; e) Mg, MeOH, RT; f) TESCl, imidazole, DMF, RT, 83% (3 steps); g) DIBALH, CH_2Cl_2, $-78\,^\circ C$; h) HOAc/THF/H_2O, RT; i) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2, RT, 78% (3 steps); j) LiHMDS, MeI, THF, $-78\,^\circ C$, 82%; k) allylmagnesium bromide, THF, $-78\,^\circ C$, 68%; l) OsO_4, *N*,*N*′-bis(2,4,6-trimethylbenzyl)-(*S*,*S*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, $-90\,^\circ C$, then aqueous $NaHSO_3$, THF, $70\,^\circ C$; m) CSA, benzene, RT, 79% (2 steps); n) NaH, BnBr, DMF, RT, 98%; o) $BF_3 \cdot OEt_2$, Me_2S, CH_2Cl_2, $0\,^\circ C$; p) $Ph_3PP^+CH_3Br^-$, NaHMDS, THF, $40\,^\circ C$; q) TESOTf, 2,6-lutidine, CH_2Cl_2, RT, 73% (3 steps); r) 9-BBN, THF, RT $\rightarrow 40\,^\circ C$, then 3 M NaOH, 30% H_2O_2, RT, 98%; s) $SO_3 \cdot$pyridine, Et_3N, CH_2Cl_2/DMSO, $0\,^\circ C$; t) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, RT; u) 0.5 M HCl, THF, RT, 55% (3 steps); v) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, benzene, reflux, 93%; w) KHMDS, $(PhO)_2P(O)Cl$ or $PhNTf_2$, THF/HMPA, $-78\,^\circ C$, 87% for **34a**, 88% for **34b**. TES = triethylsilyl, Ts = *p*-toluenesulfonyl.

29 with Me_2S and $BF_3 \cdot OEt_2$[20] effected selective cleavage of the methyl acetal portion to give a hemiacetal, which was subjected to Wittig methylenation and protection of the resulting alcohol as the TES ether to give olefin **30** in 73% overall yield. Hydroboration with 9-BBN followed by oxidative workup provided alcohol **31** (98%), which was oxidized in a two-step procedure to give, after desilylation, hydroxy acid **32** in 55% overall yield. Lactonization of **32** according to the Yamaguchi protocol yielded seven-membered lactone **33** (93%), which could be easily converted to enol phosphate **34a** in 87% yield.

With the required coupling partners **22** and **34a** in hand, we next investigated the crucial coupling reaction. However, phosphate **34a** proved to be a poor substrate for *B*-alkyl Suzuki coupling. Attempted coupling of the alkylborane derived from **22** with **34a** (aqueous 1 M $NaHCO_3$, $[Pd(PPh_3)_4]$, DMF, rt $\rightarrow 50\,^\circ C$) gave a trace of the desired coupled product **35**, and unconsumed phosphate **34a** could be recovered. After extensive investigation, it was discovered that the crucial *B*-alkyl Suzuki coupling could be accomplished by using the more reactive enol triflate **34b**, which was prepared from **33** (Scheme 4). The alkylborane derived from **22** was coupled in situ with **34b**[7a] to furnish the desired **35** in 71% yield based on **34b** (Scheme 5). Hydroboration of **35** with $BH_3 \cdot THF$ followed by oxidation led to alcohol **36** as a single stereo-



Scheme 5. Synthesis of the GHIJKLM ring system **2**. a) 9-BBN, THF, RT, then 3 M aqueous Cs_2CO_3, **34b**, $[Pd(PPh_3)_4]$, DMF, $0\,^\circ C$, 71% based on **34b**; b) $BH_3 \cdot THF$, THF, RT, then 3 M NaOH, 30% H_2O_2, RT, 81%; c) EVE, CSA, CH_2Cl_2, RT; d) TBAF, THF, RT; e) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2, RT; f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, RT; g) Ph_3SnH, AIBN, toluene, reflux, 56% (5 steps). EVE = ethyl vinyl ether.

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isomer in 81 % yield. Protection as the ethoxyethyl (EE) ether followed by desilylation and oxidation of the resulting alcohol with TPAP/NMO provided ketone **37**. Exposure of **37** to EtSH in the presence of $Zn(OTf)_2$ gave mixed thioketal **38**. Finally, radical reduction[18] of **38** furnished the target GHIJKLM ring system **2** in 56 % overall yield from **36**. The configuration of **2** was unambiguously determined by NOE experiments.

In conclusion, we have developed a highly convergent synthetic route to the GHIJKLM ring system **2** of ciguatoxin. The present synthesis demonstrates the general applicability of a strategy based on *B*-alkyl Suzuki coupling to the convergent synthesis of a polyether system. Progress toward the completion of the total synthesis of ciguatoxins is underway.

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Turning On Cell Migration with Electroactive Substrates**

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Herein we describe an electroactive substrate that was designed to turn on the migration of mammalian cells. The migration of cells is important in many developmental and disease processes that are temporally regulated.[1] Mechanistic studies of cell migration—which depend on specific interactions of cell-surface receptors with ligands of the extracellular matrix[2]—are complicated by the large number of ligands present in the matrix and the changes in ligand activity over

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