Synthesis of the H-I-J Tricyclic Fragment of Ciguatoxin, a Marine Polyether Toxin

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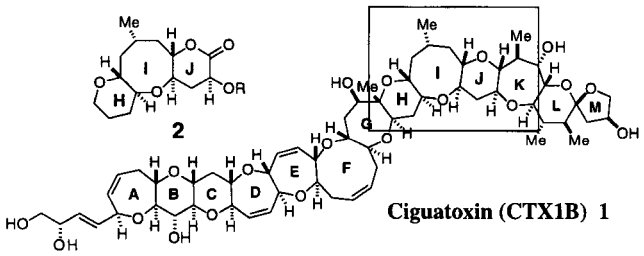
Abstract: During the course of our synthetic studies on ciguatoxin, synthesis of H-I-J tricyclic fragment has been stereoselectively achieved starting from a D-glucal derivative. The key steps are Sonogashira coupling reaction and cobalt complex-mediated oxocane cyclization.

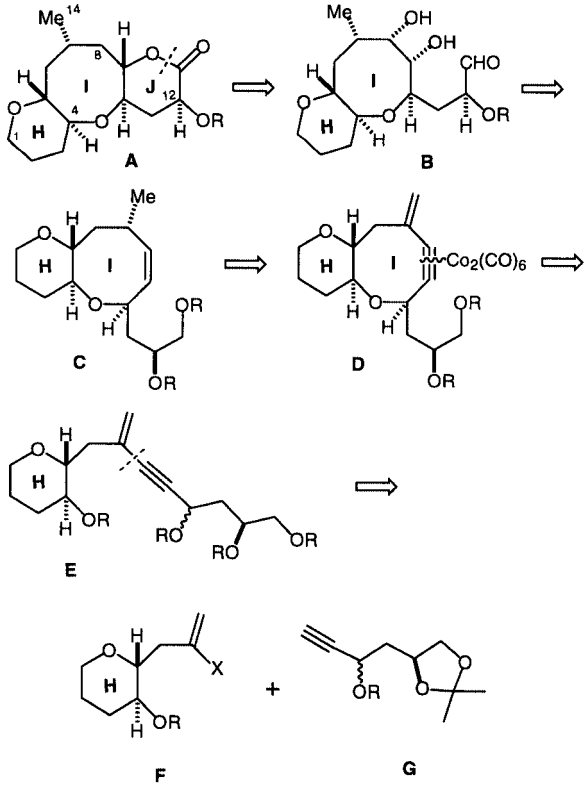
Key words: ciguatoxin, biscobalthexacarbonyl, oxocane cyclization, Sonogashira coupling

Ciguatera is one of the most widespread seafood poisonings which follows the consumption of warm water fish contaminated with sodium channel neurotoxins known as Ciguatoxin (CTX1B).[1] The complex molecular structure of CTX1B presents a formidable synthetic target molecule, particularly with regard to the construction of its *trans*-fused medium-sized ether rings.[2] During the course of our synthetic studies on ciguatoxin, we developed a synthetic methodology for the construction of medium-sized (7- to 10-membered) ether rings through cobalt complex-mediated cyclization reaction.[3] Recently, we have achieved the model study on H-I-J ring system using this methodology,[4] we now report the synthesis of H-I-J fragment **2**. The retrosynthetic analysis of H-I-J fragment **2** (**A**) is illustrated in Scheme 1.



Figure

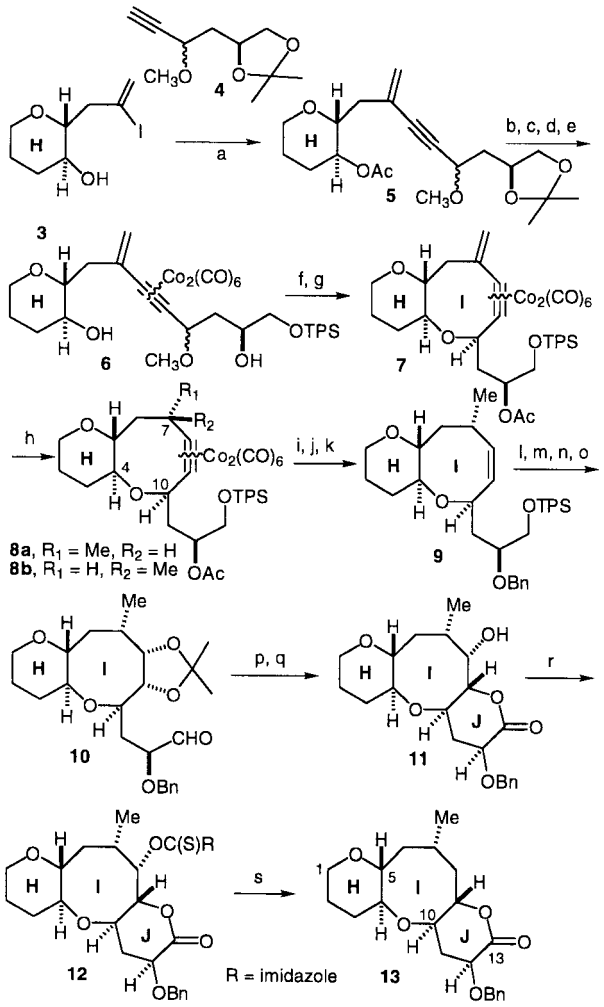
Retrosynthetic disconnection of the indicated C-O bond of J-ring in lactone **A** provides dihydroxyl aldehyde **B** as a potential precursor through a hemiacetal intermediate.[5] The *cis* dihydroxyl group in **B** would be derived from the corresponding olefin in **C** through osmium tetroxide-mediated dihydroxylation reaction.[6] Olefin **C** should be accessible from cobalt complex **D**.[7] The stereochemistry of its methyl group has to be introduced. Opening the 8-membered ring-I generates a precursor **E**. Retrosynthetic removal of the biscobalthexacarbonyl group and disconnection of the indicated bond in **E** furnishes the vinyl iodide **F** and the acetylene **G**. The stereogenic center in **G** derived from *(S)*-malic acid represents the C-12 (sugar numbering) hydroxyl group in K-ring.



Retrosynthetic Analysis of H-I-J Ring Fragment

Scheme 1

Our synthesis plan began with Sonogashira reaction to establish all the requisite carbon framework;[8] thus, coupling of the vinyl iodide **3**[3] with acetylenic chain[9] **4** in the presence of palladium(0) afforded the en-yne compound **5**. Acid-induced removal of the acetonide group, and subsequent protection of the corresponding primary alcohol as TBDPS ether were followed by deacetylation and cobalt complexation to provide the cobalt complex **6** (Scheme 2).



Reagents, conditions and yields: a) $BuNH_2$, CuI, Pd(0), benzene, r.t., 81%. b) MeOH, PPTS, 60 °C, 90%. c) TBDPSCl, Et_3N, DMF, r.t., 86%. d) MeOH, K_2CO_3, r.t., 91%. e) $Co_2(CO)_8$, CH_2Cl_2, 0 °C-r.t., 98%. f) BF_3•OEt_2, CH_2Cl_2, 0 °C, 50 min, 84%. g) Ac_2O, Py. DMAP, CH_2Cl_2, r.t., 90%. h) [HN = NH], MeOH, Et_3N, r.t., [**8a**, 68%; **8b**, 20%]. i) Bu_3SnH, toluene, 50 °C, 87%. j) MeOH, K_2CO_3, r.t., 88%. k) BnBr, NaH, DMF, -40-0 °C, 82%. l) OsO_4, NMO, acetone-H_2O (8:1), 0 °C-r.t., 80%. m) acetone, TsOH (cat), r.t., 93%. n) TBAF, THF, r.t., 89%. o) DMSO, SO_3•Py, Et_3N, 100%. p) 80% aq. AcOH, r.t., 98%. q) Br_2, DMF, NaOAc, 0 °C-r.t., 89%. r) thiocarbonyldiimidazole, $ClCH_2CH_2Cl$, reflux, 77%. s) Bu_3SnH, toluene, reflux, 88%.

Scheme 2

The cobalt complex **6** underwent smooth ring closure upon treatment with boron trifluoride etherate in degassed dichloromethane at 0 °C and acetylation to afford bicyclic compound **7** as a single stereoisomer.[10] The critical *syn* stereochemistry of **7** was demonstrated by NOESY experiments. The observation of cross peaks between H-4 (δ 3.08, ddd, J = 11.0, 9.5, 4.8 Hz) and H-10 (δ 4.79, dd, J = 10.0, 3.0 Hz) indicated a *syn* relationship between these protons. Reduction of the exo-cyclic olefin in **7** with diimide[11] afforded a 3:1 mixture of diastereoisomers **8a** and **8b**, epimeric at C-7 (sugar numbering), which could be separated by silica gel chromatography. The configuration of the newly-formed methyl group was determined by comparison the NOESY data of these two compounds.[12]

Reductive decomplexation of **8a**, and subsequent conversion of the acetyl into benzyl group furnished the *cis* olefin **9**. Dihydroxylation of this olefin **9** with OsO_4 in acetone[5] yielded a diol intermediate which was converted to the corresponding acetonide, from which subsequent removal of the TBDPS group and oxidation of the alcohol afforded the corresponding aldehyde **10**. Acidic hydrolysis of the acetonide group of **10** ended up with a subsequent ring-J formation in one step to afford a hemiacetal intermediate, which was further transformed to the corresponding lactone **11** through bromine oxidation. The secondary hydroxyl group on the I-ring was removed in 2 steps including 1) treatment of **11** with N,N'-thiocarbonyldiimidazole[13] in refluxing 1,2-dichloroethane to provide the thioester **12** and 2) Barton's deoxygenation of **12** with tri-*n*-butyltin hydride[14] in refluxing toluene. The lactone **13**[15] showed the coupling constant ($J_{9,10}$ = 9.5 Hz) between the protons at the junction to indicate the *trans* stereochemistry.

We have accomplished the synthesis of the H-I-J tricyclic fragment directed toward the construction of the right hand part of ciguatoxin. Further synthetic studies on the construction of H-I-J-K ring fragment along this line are now in progress and will be reported.

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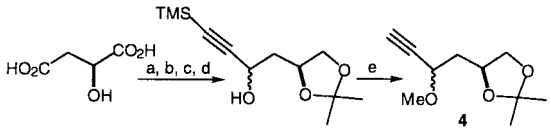
(9) Compound **4** was synthesized as follows:



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Reagents, conditions and yields: a) BH_3•SMe_2, $B(OMe)_3$, THF, 0 °C, then MeOH workup. b) acetone, TsOH (cat), r.t., 81% (2 steps). c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78-0 °C. d) trimethylsilylacetylene, *n*-BuLi, THF, -78-0 °C, 53% (2 steps). e) DMSO, KOH powder, CH_3I, 82%.

(10) Selected data of compound **7**: $[\alpha]_D^{26}$+26.0 (c 0.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24-1.31 (1H, m, H-3a), 1.53-1.56 (2H, m, H-2 x 3), 1.79 (1H, br d, *J* = 11.8, H-3b), 1.95 (1H, ddd, *J* = 14.2, 10.0, 5.2 Hz, H-11a), 2.06 (3H, s, CH_3CO), 2.39 (1H, ddd, *J* = 14.2, 10.0, 2.6 Hz, H-11b), 2.61 (1H, dd, *J* = 14.0, 2.0 Hz, H-6a), 2.72 (1H, dd, *J* = 14.0, 4.5 Hz, H-6b), 3.08 (1H, ddd, *J* = 11.0, 9.5, 4.8 Hz, H-4), 3.25-3.33 (2H, m, H-1a, H-5), 3.78 (1H, dd, *J* = 12.0, 4.0 Hz, H-13a), 3.83 (1H, dd, *J* = 12.0, 4.0 Hz, H-13b), 3.89 (1H, dt, *J* = 11.8, 2.5 Hz, H-1b), 4.79 (1H, dd, *J* = 10.0, 3.0 Hz, H-10), 5.28 (1H, m, H-12), 5.42 (1H, d, *J* = 1.5 Hz, C=CH_2), 5.54 (1H, d, *J* = 2.0 Hz, C=CH_2), 7.35-7.43 (6H, m, Ph), 7.65-7.69 (4H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.1, 21.2, 22.6, 26.6, 30.3, 31.5, 38.5, 40.3, 64.4, 7.9, 72.3, 77.2, 79.3, 80.4, 121.5, 127.8, 129.8, 133.1, 133.3, 135.6, 135.7, 141.2, 170.4, 199.7. MS (MALDI-TOF): calcd for $C_{38}H_{41}Co_2O_{11}Si$ m/z $[M+H]^+$, 819.11; found, m/z 819.20.
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(15) Data of the lactone **13**: mp (°C):127-129. $[\alpha]_D^{27}$ -59.2 (c 0.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, d, *J* = 7.0 Hz, CH_3), 1.45-1.52 (1H, m, H-3a), 1.59-1.69 (4H, m, H-2 x 2, H-6a, H-8a), 1.79-1.92 (2H, m, H-6b, H-7), 2.03-2.10 (3H, m, H-3b, H-8b, H-11a), 2.39 (1H, dt, *J* = 13.8, 7.8 Hz, H-11b), 3.05 (1H, td, *J* = 10.0, 2.8 Hz, H-5), 3.15 (1H, td, *J* = 10.0, 4.8 Hz, H-4), 3.23-3.31 (1H, m, H-1a), 3.64 (1H, td, *J* = 9.5, 6.0 Hz, H-10), 3.83 (1H, br d, *J* = 11.0 Hz, H-1b), 3.95 (1H, dd, *J* = 8.5, 6.0 Hz, H-12), 4.35 (1H, ddd, *J* = 11.0, 9.5, 3.5 Hz, H-9), 4.66 (1H, d, *J* = 12.0 Hz, $PhCH_2O$), 4.89 (1H, d, *J* = 12.0 Hz, $PhCH_2O$), 7.30-7.39 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 27.8, 32.4, 36.2, 45.2, 45.6, 67.5, 72.1, 72.3, 80.1, 81.9, 82.0, 85.3, 128.1, 128.5, 137.2, 169.8. IR (KBr): ν_{max} 1749, 1685, 1508, 1458, 1266, 1181, 1115, 947 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.14; H, 8.02.

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