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Convergent Synthesis of the E′FGH′ Ring Fragment of Ciguatoxin 1B via an Acetylene Cobalt Complex Strategy

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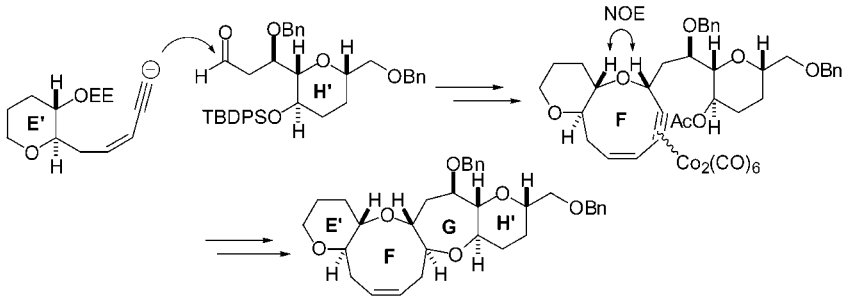
ABSTRACT



A convergent synthesis of the E′FGH′ ring fragment of ciguatoxin has been accomplished through (i) coupling between the E′ ring-acetylide and the H′ ring-aldehyde, (ii) stereoselective F ring cyclization via an acetylene cobalt complex, (iii) conversion to a carbonyl function, and (iv) reductive hydroxy-ketone cyclization to construct the G ring.

Ciguatoxin 1B (CTX 1B, **1**)[1] is one of the most toxic marine natural products causing seafood poisoning "ciguatera". Several synthetic groups[2] have been involved in the total synthesis of CTX due to its remarkable structural complexity, biological activity, and limited availability from nature. Recently, Hirama's group reported the first total synthesis of CTX-3C,[2a] a member of the CTX family.[1d]

During the course of our synthetic studies toward **1**, various methodologies have been developed on the basis of (i) construction of medium-size (7−10) ether rings via acetylene cobalt complexes in a highly stereoselective *syn-trans* mode,[3] (ii) reductive decomplexation reaction into *cis*-olefins or vinylsilanes,[4] (iii) ring-opening reactions of cyclic α,β-epoxysilanes into allyl alcohols,[5] and (iv) stereoselective heteroconjugate additions.[6] We have already reported the model syntheses of the ABC,[7] BCDE,[8] D′EF,[9] and HIJK rings.[10]

Scheme 1 exhibits retrosynthetic analysis toward **1**, where the A, F, and G ring cyclization would be achieved at the last stage from **2** that would be synthesized through a

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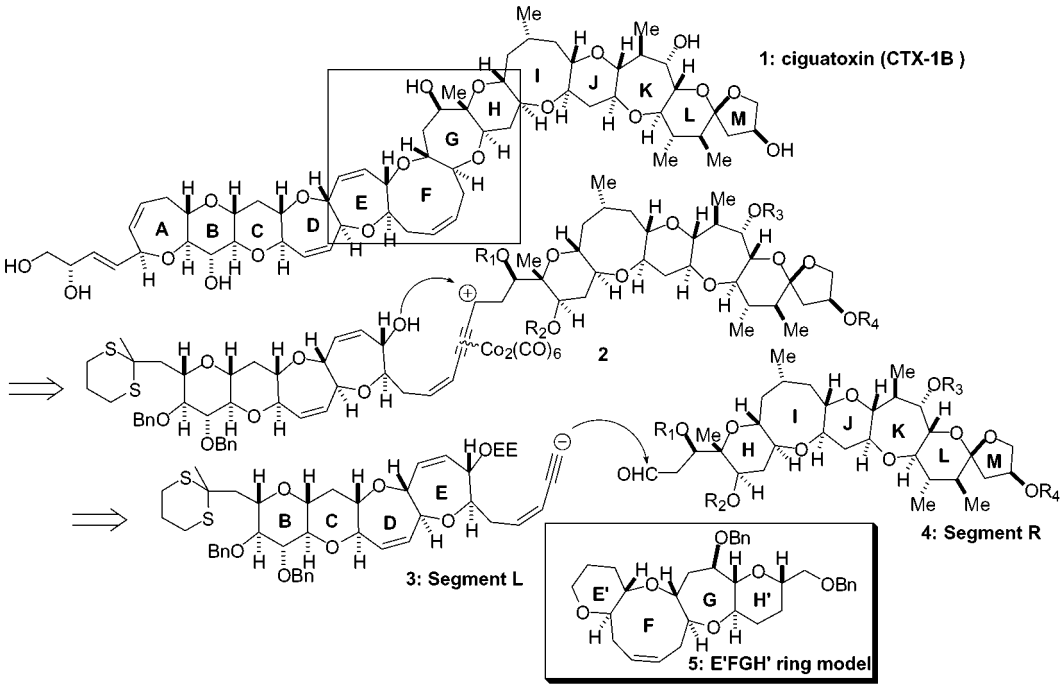
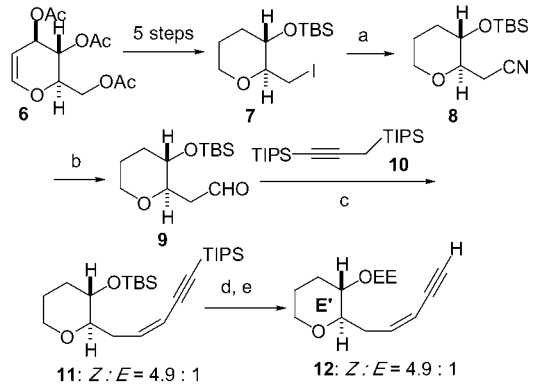
Scheme 1



coupling between acetylide **3** (Segment L) and aldehyde **4** (Segment R). On the basis of this analysis, we planned the synthesis of **5** as a model of the E′FGH′ ring.[11] In this paper, we describe the convergent synthesis of **5**, which means not only a partial synthesis but also a virtual synthesis in the last stage toward CTX **1**.

An E′ ring-enyne as a model of Segment L **3** was synthesized as shown in Scheme 2. A nitrile group was introduced to the primary iodide **7**, prepared from tri-*O*-acetyl-D-glucal in five steps in a known procedure[12] to give **8**. After DIBAL reduction of **8**, the product aldehyde **9** was further converted into **11** by Peterson-type olefination[13] in 73% yield (*Z*:*E* = 4.9:1). Finally, protective group manipulations afforded E′ ring-enyne **12**.

Scheme 2[a]



[a] Synthesis of E′ ring-enyne. (a) NaCN, DMSO, 80 °C, 85%; (b) DIBAL, toluene, −78 °C, 58%; (c) **10**, *n*-BuLi, THF, from −78 to 0 °C, and then **9**, −78 °C, 73%; (d) TBAF, THF, 94%; (e) EVE, PPTS, CH_2Cl_2, 97%.

The counter H′ ring-aldehyde as a model of Segment R **4** was synthesized as shown in Scheme 3. 2-Acetoxy-D-glucal **13** was consecutively subjected to *C*-glycosidation,[14] Luche reduction,[15] and protection to give α-acetylene **14**, which was epimerized into more stable *β*-acetylene **15** via an acetylene cobalt complex exclusively.[16] Elongation of the C-1 unit by acetylide coupling with formaldehyde gave propargyl alcohol **16** followed by hydroaluminative *trans*

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(12) (1) Et_3SiH, BF_3·OEt_2, CH_2Cl_2; (2) Et_3N, MeOH, H_2O; (3) H_2, Pd/C, MeOH; (4) I_2, PPh_3, imidazole, Et_2O, CH_3CN; (5) TBSCl, imidazole, DMF.

(13) Corey, E. J.; Ruker, C. *Tetrahedron Lett.* **1982**, *23*, 719−722.

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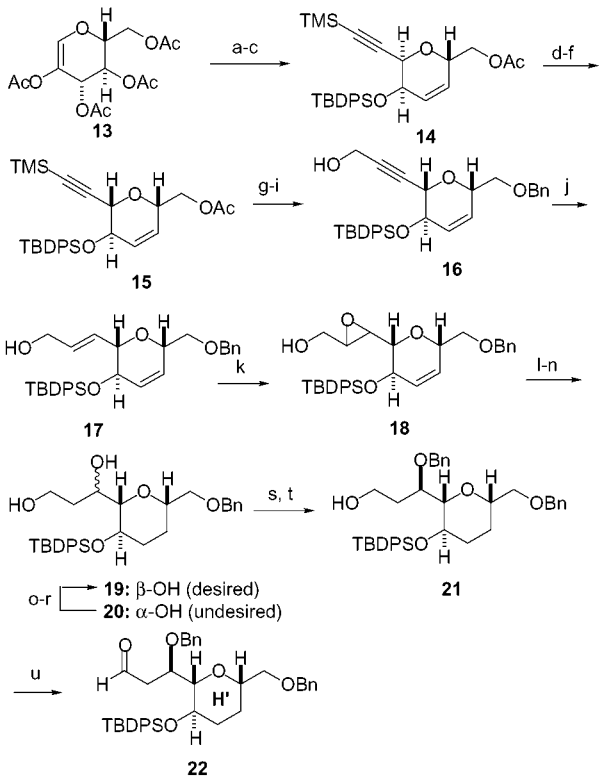
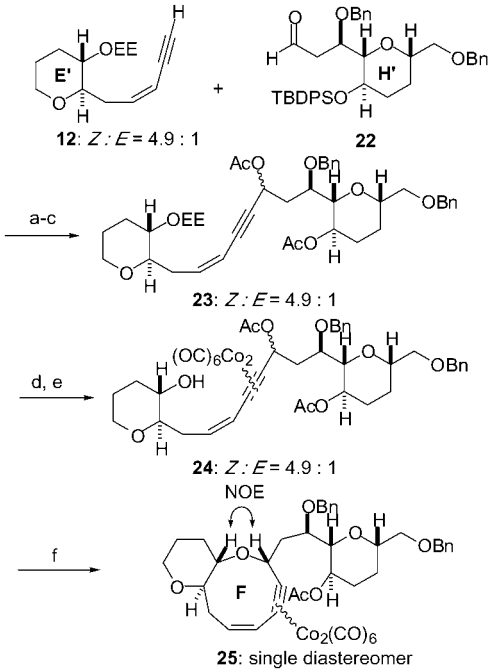
Scheme 3[a]



[a] Synthesis of H′ ring-aldehyde **22**. (a) Bistrimethylsilylacetylene, $SnCl_4$, CH_2Cl_2, −20 °C; (b) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 86% in two steps; (c) TBDPSCl, imidazole, DMF, 100%; (d) $Co_2(CO)_8$, CH_2Cl_2, rt; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, from 0 °C to rt; (f) I_2, THF, 92% in three steps; (g) K_2CO_3, MeOH, 99%; (h) BnCl, KOH, 90 °C, 87%; (i) *n*-BuLi, THF, $(HCHO)_n$, from −78 to 0 °C, 85%; (j) Red-Al, 0 °C, THF, 95%; (k) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C; (l) Red-Al, toluene, 0 °C, 86% (1:1) in two steps; (m) H_2, 10% Pd/C, $NaHCO_3$, EtOH, 100%; (n) separation; (o) TBSCl, imidazole, DMF, 92%; (p) IBX, DMSO, 82%; (q) DIBAL, CH_2Cl_2, −78 °C, 83% (95:5); (r) CSA, MeOH, 0 °C, 100%; (s) Ph-$CH(OMe)_2$, CSA, CH_2Cl_2, 99%; (t) $BH_3{\cdot}$THF, reflux, 89%; (u) IBX, DMSO, 92%.

reduction to give allyl **17**. In the next step, Sharpless asymmetric epoxidation[17] was very sluggish (TBHP, Ti-$(OPr^i)_4$, (+)-DET, CH_2Cl_2, −23 °C, 12 h) in 30% yield as a single diastereomer. Therefore, *m*CPBA oxidation was followed by Red-Al reduction and hydrogenation to furnish the desired **19** and undesired **20** in 86% overall yield as a 1:1 mixture of two diastereomers. The undesired diastereomer **20**, however, was reusable in the following procedure; thus, temporary protection of the primary alcohol by the TBS group, IBX oxidation,[18] DIBAL reduction, and deprotection of the TBS group occurred. IBX oxidation of primary alcohol **21** resulting from a protection of secondary alcohol **19** by way of BH_3 reduction[19] of benzylidene acetal afforded H′ ring-aldehyde **22**.

Scheme 4[a]



[a] Coupling and F ring cyclization. (a) **12** (1.5 equiv), *n*-BuLi, THF, −78 °C, and then **22**, 86%; (b) TBAF, THF; (c) Ac_2O, Py, DMAP, CH_2Cl_2, 96% in two steps; (d) PPTS, MeOH; (e) $Co_2(CO)_8$, CH_2Cl_2, 96% in two steps; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, from 0 °C to rt over 30 min, 77%.

With the coupling precursors, i.e., E′ ring-enyne **12** and H′ ring-aldehyde **22**, in hand, we tried the coupling reaction to provide propargyl alcohol in 86% yield as shown in Scheme 4. In addition, protecting group manipulation and installation of a cobalt complex gave **24** as a precursor of cyclization. Treatment of acetylene cobalt complex **24** with $BF_3{\cdot}OEt_2$ at room-temperature effected the F ring cyclization in 77% yield to afford a single diastereomer **25** (on the other hand, the (*E*)-isomer of **24** could not be cyclized). The *syn* stereochemistry of **25** was determined by a NOE experiment.

Scheme 5 illustrates the final stage of the current strategy toward the E′FGH′ ring synthesis. In the course of substantial trials and errors in regard to the conversion of the acetylene cobalt complex moiety into ketone, we found a novel reaction under high-pressure hydrogenation,[20] where acetylene cobalt complex **25** gave rise to the desired ketone **26** in 37% yield as a major compound along with conjugated enone **27** (4%) and diene **28** (15%). This reaction mechanism, however, has not been proven in detail yet. With the precursor **26** of the G ring cyclization in hand, we treated **26** with K_2CO_3 in MeOH and $BF_3{\cdot}OEt_2$ in the presence of Et_3SiH in CH_3CN[21] to accomplish the stereoselective construction of the E′FGH′ ring **5** as a white solid in 57% yield. In the ^1H NMR analysis

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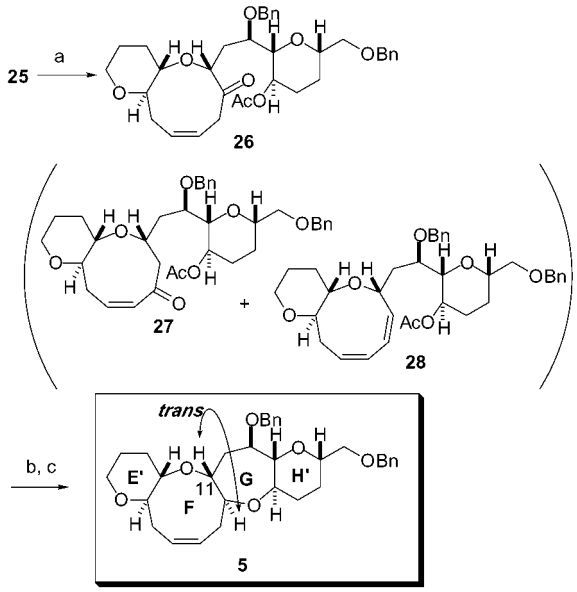
Scheme 5[a]



[a] G ring cyclization. (a) H_2, 100 kg/cm^2, benzene, 65 °C, 6 h, **26** (37%), **27** (4%), **28** (15%); (b) K_2CO_3, MeOH, 100%; (c) BF_3·OEt_2, Et_3SiH, CH_3CN, from −15 °C to rt over 30 min, 57%.

at room temperature, a considerable broadening phenomenon was observed due to the slow conformational changes of the F ring, as reported for natural product CTX[1b] and other model systems.[10c,11,22] When the NMR measurement of **5** was carried out in $CDCl_3$ at −20 °C, the spectrum exhibited a 2:1 mixture of two conformational isomers (DOWN and UP conformers, whose olefinic bonds are located below the down side or above the up side of the ring plane, respectively) as sharp signals. Comparison of the observed coupling constants of $^3J_{5,6}$ and $^3J_{9,10}$ with those of energy-minimized conformers by Macromodel (MM2* force field) should predict the majority to be the DOWN conformer as shown in Figure 1. Although the *syn* stereochemistry between H-10 and H-15 could not be determined directly by NOE experiments, the fact that the coupling constants between H-10 and H-11 showed 9.5 Hz for the DOWN conformer and 11.0 Hz for the UP conformer undoubtedly demonstrated the *trans* stereochemistry of **5**.

In conclusion, we have accomplished the synthesis of an E′FGH′ ring model fragment of CTX in a convergent manner

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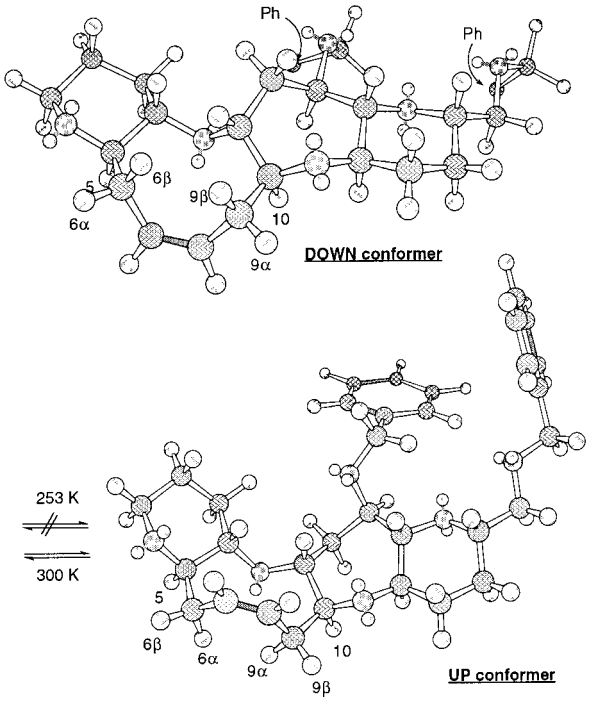

DOWN	calcd	found
$^3J_{5,6\beta}$	10.9 Hz	9.5 Hz
$^3J_{5,6\alpha}$	1.4 Hz	~0 Hz
$^3J_{9\beta,10}$	11.3 Hz	9.5 Hz
$^3J_{9\alpha,10}$	1.8 Hz	~0 Hz

UP	calcd	found
$^3J_{5,6\beta}$	1.8 Hz	~0 Hz
$^3J_{5,6\alpha}$	5.3 Hz	5.5 Hz
$^3J_{9\beta,10}$	2.3 Hz	~0 Hz
$^3J_{9\alpha,10}$	4.5 Hz	5.0 Hz

Figure 1. DOWN and UP conformers of the E′FGH′ ring **5** and their coupling constants at −20 °C in $CDCl_3$.

through the coupling between E′ ring-enyne and H′ ring-aldehyde, highly stereoselective cyclization of the F ring using an acetylene cobalt complex, and a novel conversion of the acetylene cobalt complex into the ketone followed by reductive cyclization of the G ring. Further studies toward the total synthesis of CTX are now in progress and will be published elsewhere.

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Supporting Information Available: Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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