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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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A convergent synthesis of the E′FGH ring fragment **28** of ciguatoxin 1B, a principal toxin causing widespread seafood poisonings "ciguatera", has been accomplished through (i) coupling between the E′ ring-acetylide **9** and the H ring-aldehyde **20**, (ii) stereoselective F ring cyclization via an acetylene cobalt complex, (iii) conversion to a carbonyl function under high-pressure hydrogenation, and (iv) reductive hydroxyketone cyclization to construct the G ring. In the ^{1}H NMR analysis of **28** at room temperature, a considerable broadening phenomenon was observed due to the slow conformational changes of the FG ring, as reported for natural ciguatoxin 1B. When measured in pyridine at −20 °C, the spectra of **28** exhibited a 3.5:1 mixture of two conformational isomers (UP and DOWN conformers).

Introduction

Ciguatoxin (recently called CTX1B, **1**) is a principal toxin causing ciguatera, which is one of the most widespread seafood poisonings (Scheme 1).[1] Ciguatoxin **1** and its congeners are produced by the epiphytic dinoflagellate *Gambierdiscus toxicus*[2] and transferred through the food chain among coral biota and accumulated in carnivorous fish, thus causing human intoxication. It is a major problem in the Pacific and Indian Oceans and the Caribbean Sea, where roughly 20 000 people are affected annually.[1] Ciguatoxins are potent neurotoxins that bind quasi-irreversibly to site 5 on the voltage-sensitive sodium channels (VSSC).[3] However, the mechanism for the binding mode of ciguatoxins to the channel protein has not been elucidated. The binding site on VSSC was reported to be shared by brevetoxins or another class of structurally related marine toxins.[4]

Ciguatoxin **1** was first isolated from moray eel, *Gymnothorax javanicus*, by Scheuer and co-workers at the University of Hawaii in 1967 and characterized as a polyether compound in 1980.[5] The gross structure, except the absolute configuration and the relative one at C2 position, was elucidated by Yasumoto and co-workers in 1989 using a purified sample of only 0.35 mg.[6] The absolute configuration was determined by Yasumoto and co-workers in 1997 as shown in Scheme 1.[7] Despite structural similarity to brevetoxins, the binding affinity of **1** was shown to be some 10 times more potent than that of brevetoxins. The activity of **1** remains one of the most potent neurotoxins known with mice lethality LD_{50} of 0.35 μg/kg (i.p.).[3]

The striking constitution of **1** presents a formidable challenge to organic synthesis. The unique and fascinating molecular architecture of **1**, its association with fish poisoning, its potent biological activity, the limited availability of the compound from nature, and the prospects for expanding the arsenal of synthetic methods all contributed to our decision to pursue a total synthesis of **1**.[8] Recently, Hirama's group reported the first total synthesis of CTX3C, a member of the CTX family.[9]

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* orientation,[10] (ii) reductive decomplexation reaction into *cis*-olefins or vinylsilanes,[11] (iii) ring-opening reac-

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(1) For reviews, see: (a) Gillespie, N. C.; Lewis, R. J.; Pearn, J.; Bourke, A. T. C.; Helms, M. J.; Bourke, J. B.; Shields, W. J. *Ned. J. Aust.* **1986**, *145*, 584−590. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909. (c) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3−18. (d) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228−242.

(2) Yasumoto, T.; Nakajima, R.; Bagnis, R.; Adachi, R. *Nippon Suisan Gakkaishi* **1977**, *43*, 1021−1023.

(3) (a) Lombert, A.; Bidard, J.-N.; Lazdunski, M. *FEBS Lett.* **1987**, *219*, 355−359. (b) Lewis, R. J.; Sellin, M.; Poli, M. A.; Norton, R. S.; Macleod, J. K.; Sheil, M. M. *Toxicon* **1991**, *29*, 1115−1127. (c) Dechraoui, M.-Y.; Naar, J.; Pauillac, S.; Legrand, A.-M. *Toxicon* **1999**, *37*, 125−143. (d) Anger, T.; Madge, D.-J.; Mulla, M.; Riddall, D. *J. Med. Chem.* **2001**, *44*, 115−137.

(4) (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773−6776. (b) Shimizu, Y.; Chou, H.-N.; Bando, H.; Duyne, G. V.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514−518.

(5) (a) Scheuer, P. J.; Takahashi, W.; Tsutsumi, J.; Yoshida, T. *Science* **1967**, *155*, 1267−1268. (b) Tachibana, K. Ph.D. Thesis, University of Hawaii, 1980.

(6) (a) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929−8931. (b) Murata, M.; Legrand, A. M.; Yasumoto, T. *Tetrahedron Lett.* **1989**, *30*, 3793−3794. (c) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380−4386. (d) Murata, M.; Legrand, A. M.; Scheuer, P. J.; Yasumoto, T. *Tetrahedron Lett.* **1992**, *33*, 525−526.

(7) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11325−11326.

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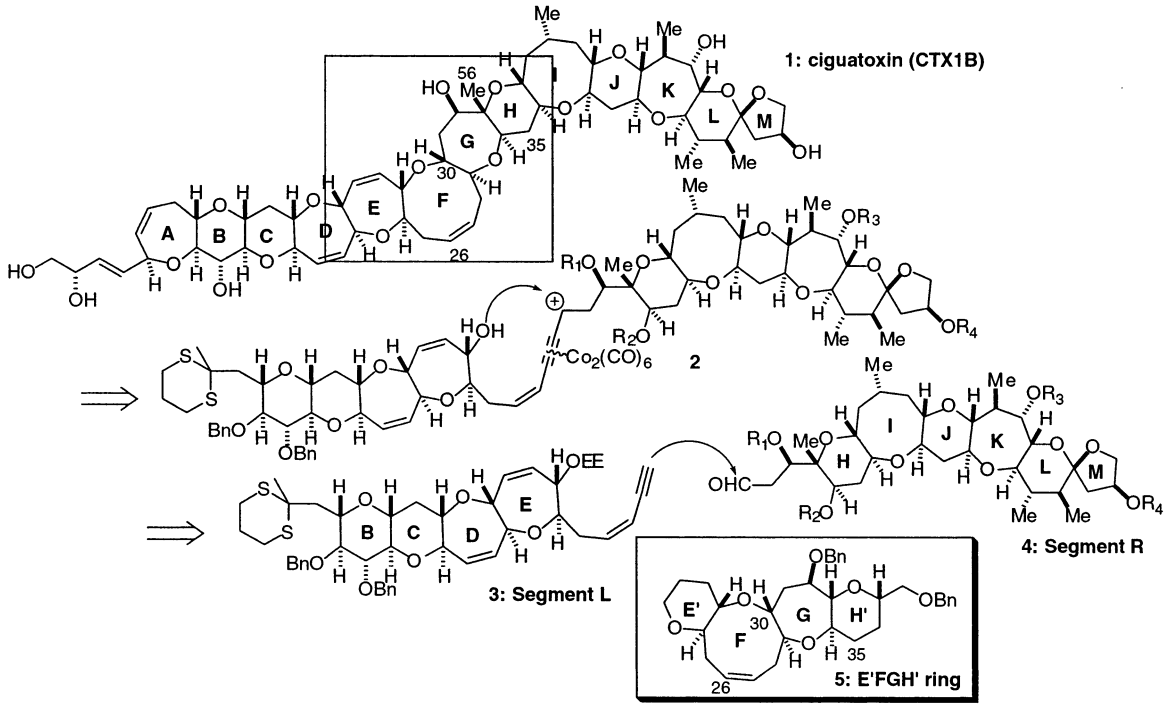
SCHEME 1. Retrosynthetic Analysis toward CTX1B



tions of cyclic α,β-epoxysilanes into allyl alcohols,[12] and (iv) stereoselective heteroconjugate additions.[13] We have already reported the model syntheses of the ABC,[14] BCDE,[15] D′EF,[16] H′IJK,[17] and E′FGH′ ring fragments.[18] In this paper, we describe the convergent synthesis of E′FGH′ ring **5** (without an angular methyl group corresponding to the C56 position) and E′FGH ring **28** (with an angular methyl group) using these methodologies, which means not only a partial synthesis but also a virtual synthesis in the last stage toward **1**.

Results and Discussion

Scheme 1 exhibits retrosynthetic analysis toward **1**, where the A, F, and G ring would be cyclized at the latest stage from **2** after the coupling between acetylide of **3** (segment L) and aldehyde **4** (segment R). On the basis of this analysis, we planned the synthesis of model compound **5** for the E′FGH′ ring first without the angular methyl group corresponding to the C56 position.[19]

Scheme 2 shows retrosynthetic analysis of **5**. The G ring cyclization would be achieved from hydroxyvinylsilane **6**, where the hydroxyl group would attack at the β carbon to the silyl atom due to its electrophilicity under either acidic or basic condition. Hydroxyvinylsilane **6** should be derived from acetylene cobalt complex **7**. Retrosynthetic disconnection of F ring of **7** gives **8**, which should be prepared by the coupling reaction between acetylide of **9** and aldehyde **10**.[20]

(8) For recent synthetic studies from other groups, see: (a) Uehara, H.; Oishi, T.; Inoue, M.; Shoji, M.; Nagumo, Y.; Kosaka, M.; Le Brazidec, J.-Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 6493−6512. (b) Takakura, H.; Sasaki, M.; Honda, S.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2771−2774. (c) Fujiwara, K.; Koyama, Y.; Kawai, K.; Tanaka, H.; Murai, A. *Synlett* **2002**, 1835−1838. (d) Bond, S.; Perlmutter, P. *Tetrahedron* **2002**, *58*, 1779−1787. (e) Leeuwenburgh, M. A.; Kulker, C.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1999**, 1945−1947. (f) Candenas, M. L.; Pinto, F. M.; Cintado, C. G.; Morales, E. Q.; Brouard, I.; Díaz, M. T.; Rico, M.; Rodríguez, E.; Rodríguez, R. M.; Pérez, R.; Pérez R. L.; Martín, J. D. *Tetrahedron* **2002**, *58*, 1921−1942. (g) Soler, M.-A.; Palazón, J.-M.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5471−5474. (h) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372−374 and references therein.

(9) (a) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904−1907. (b) Inoue, M.; Uehara, H.; Maruyama, M.; Hirama, M. *Org. Lett.* **2002**, *4*, 4551−4554.

(10) (a) Isobe, M.; Yenjai, C.; Tanaka, S. *Synlett* **1994**, *11*, 916−918. (b) Yenjai, C.; Isobe, M. *Tetrahedron* **1998,** *54*, 2509−2520. (c) Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.* **1996**, 473−474. (d) For a review, see; Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665−2676.

(11) (a) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609−2612. (b) Shibuya, S.; Isobe, M. *Tetrahedron* **1998**, *54*, 6677−6698. (c) Takai, S.; Ploypradith, P.; Hamajima, A.; Kira, K.; Isobe, M. *Synlett* **2002**, 588−592.

(12) Kira, K.; Isobe, M. *Chem. Lett.* **2001**, 432−433.

(13) (a) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, *20*, 3465−3468. (b) Isobe, M.; Funabashi, Y.; Ichikawa, Y.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 2021−2024. (c) Perspectives in the Organic Chemistry of Sulfur. Zwanenburg, B., Klunder, A. J. H., Eds. New Synthetic Methods Using Vinyl Sulfones−Developments in Heteroconjugate Addition. Isobe, M. *Studies Org. Chem.* **1987**, *28*, 209−229.

(14) (a) Hosokawa, S.; Isobe, M. *Synlett* **1995**, 1179−1180. (b) Hosokawa, S.; Isobe, M. *Synlett* **1996**, 351−352. (c) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37−48. (d) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911−1914. (e) Saeeng, R.; Isobe, M. *Heterocycles* **2001**, *54*, 789.

(15) (a) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821−2824. (b) Kira, K.; Hamajima, A.; Isobe, M. *Tetrahedron* **2002**, *58*, 1875−1888.

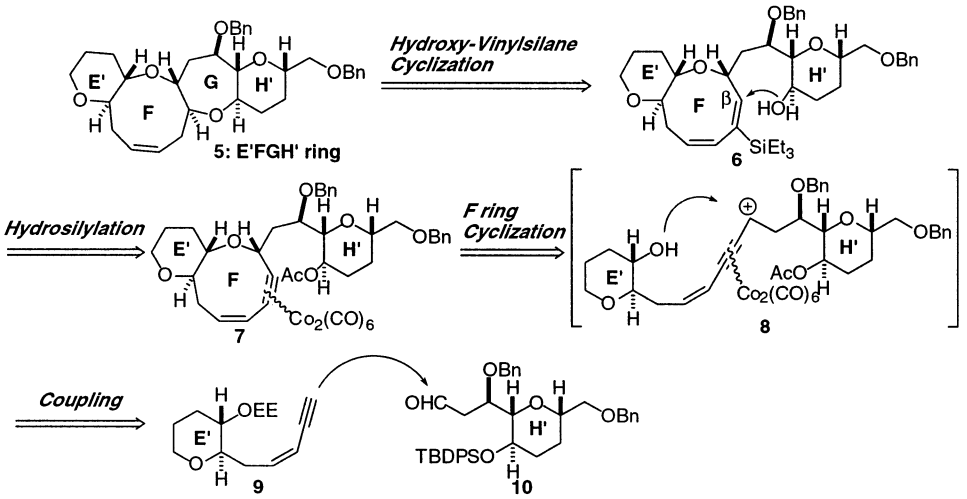
(16) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2000**, *41*, 5951−5955.

(17) (a) Liu, T.-Z.; Isobe, M. *Synlett* **2000**, 587−589. (b) Liu, T.-Z.; Isobe, M. *Tetrahedron* **2000**, *56*, 5391−5404. (c) Liu, T.-Z.; Li, J.-M.; Isobe, M. *Tetrahedron* **2000**, *56*, 10209−10219. (d) Liu, T.-Z.; Isobe, M. *Synlett* **2000**, 266−268.

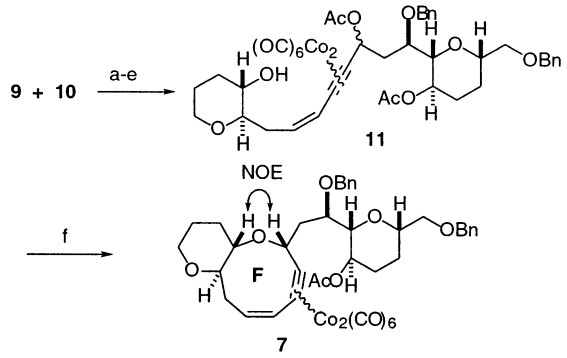
(18) Takai, S.; Isobe, M. *Org. Lett.* **2002**, *4*, 1183−1186.

(19) Synthesis of another model system of the EFGH ring: (a) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337−1340. (b) Imai, H.; Uehara, H.; Inoue, M.; Oguri, H.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **2001**, *42*, 6219−6222. (c) Sasaki, M.; Noguchi, T.; Tachibana, K. *J. Org. Chem.* **2002**, *67*, 3301−3310. (d) Inoue, M.; Wang, G. X.; Wang, J.; Hirama, M. *Org. Lett.* **2002**, *4*, 3439−3442.

SCHEME 2. Retrosynthetic Analysis of E′FGH′ Ring 5



SCHEME 3[a]



[a] Segment coupling and F ring cyclization: (a) **9** (1.5 equiv), *n*-BuLi, THF, −78 °C then **10**, 86% (recovered **10**: 14%); (b) TBAF, THF; (c) Ac_2O, Py, DMAP, CH_2Cl_2, 99% in two steps; (d) PPTS, MeOH, 100%; (e) $Co_2(CO)_8$, CH_2Cl_2, 99%; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 30 min, 77%.

As shown in Scheme 3, the coupling reaction between **9** and **10**, in fact, provided a propargyl alcohol in 86% yield and protecting group manipulation followed by conversion to a cobalt complex gave **11** as a precursor of cyclization in four steps. Treatment of acetylene cobalt complex **11** with $BF_3{\cdot}OEt_2$ at room temperature effected the F ring cyclization in 77% yield to afford a single diastereomer **7** under a thermodynamic condition with the acid at 10 mM for half an hour. The stereochemistry of **7** was determined to be *syn* by an NOE experiment.

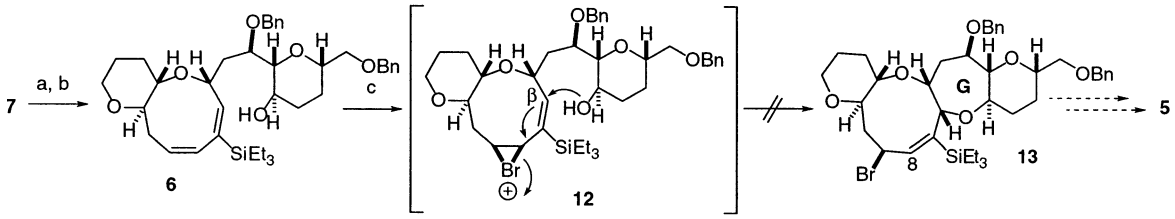
Acetylene cobalt complex **7** was subjected to hydrosilylation by heating in the presence of trapping agent, bis(trimethylsilyl)acetylene,[21] for the active cobalt residues and deprotection of acetate to give **6** as a precursor of G ring cyclization (Scheme 4). Judging from conformational analysis based on ^{1}H NMR data of a product from **6** exposed to condition (c), it seemed likely that TBCO (2,4,4,6-tetrabromo-2,5-cyclohexadienone)[22] would attack from β side of the disubstituted olefin of **6** followed by intramolecular S_N2' reaction at the β carbon to silyl atom to afford tetracyclic compound **13**. Extensive NMR analyses (NOESY, HMBC, etc.) of the product, however, indicated a much different compound **15** via transannular reaction, where the lone pair of ether oxygen in F ring of **12** would attack at the β' carbon to give intermediate **14** followed by 6-*exo* recyclization (Scheme 5).

Due to the difficulty in preventing from the transannular reaction, we revised retrosynthetic analysis for E′FGH′ ring **5** as shown in Scheme 6. Retrosynthetic disconnection of G ring in **5** could provide hydroxyketone **16** as a reliable precursor, which could be converted from acetylene cobalt complex **7** in one step, though it was known that high-pressure hydrogenation of an acetylene cobalt complex in F ring gave the corresponding ketone in moderate yield.[23]

Scheme 7 illustrates the final stage of the current strategy toward the E′FGH′ ring synthesis. High-pressure hydrogenation of **7** without any catalyst gave rise to the desired ketone **17** in 37% yield as a major compound along with conjugate enone **18** (4%) and diene **19** (15%).[24] After deacetylation of **17**, hydroxyketone **16** was treated with $BF_3{\cdot}OEt_2$ in the presence of Et_3SiH in CH_3CN[25] to accomplish the stereoselective construction of the E′FGH′ ring **5** in 57% yield.[18] In the ^{1}H NMR analysis of **5** at room temperature, a considerable broadening phenomenon was observed due to the slow conformational changes of the FG ring, as reported for natural product CTX1B[6,26] and other model systems.[19,27] When measured in $CDCl_3$ at −20 °C, the spectra of **5** 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 (Figure 1 and Figure 2).[28]

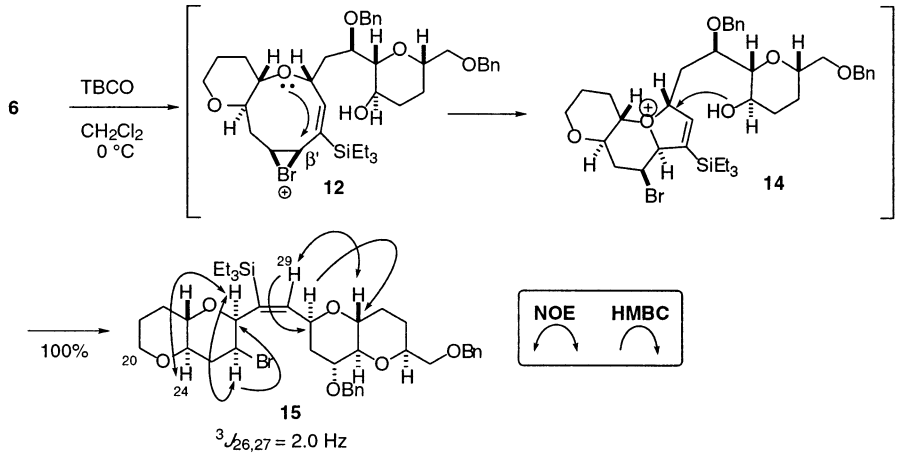
(20) Synthetic route and data of **9** and **10** were reported in ref 18.
(21) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485−6492.
(22) Kato, T.; Ichinose, I.; Hosogai, T.; Kitahara, Y. *Chem. Lett.* **1976**, 1187.
(23) Kira, K.; Isobe, M. *J. Synth. Org. Chem., Jpn.* **2000**, *58*, 23−30.
(24) This reaction mechanism, however, has not been proven in detail yet.
(25) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.
(26) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380−4386.
(27) Conformational change of another model system: (a) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **1997**, *38*, 1611−1614. (b) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron* **1999**, *55*, 10949−10970.

SCHEME 4[a]



[a] Attempt to cyclize G ring: (a) Et_3SiH, bis(trimethylsilyl)acetylene, 1,2-dichloroethane, 60 °C, 81%; (b) K_2CO_3, MeOH, 95%; (c) TBCO, CH_2Cl_2, 0 °C, 100%.

SCHEME 5. Transannular Reaction



SCHEME 6. Revised Retrosynthetic Analysis for E′FGH′ Ring 5

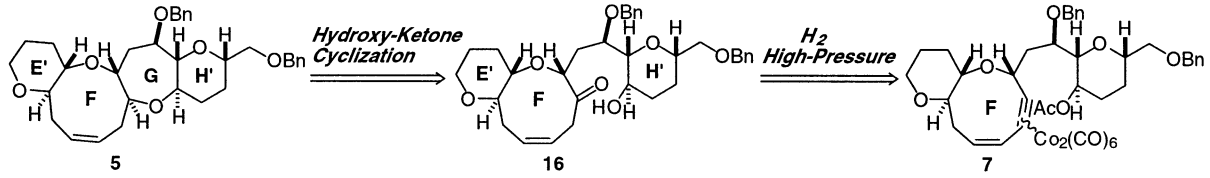
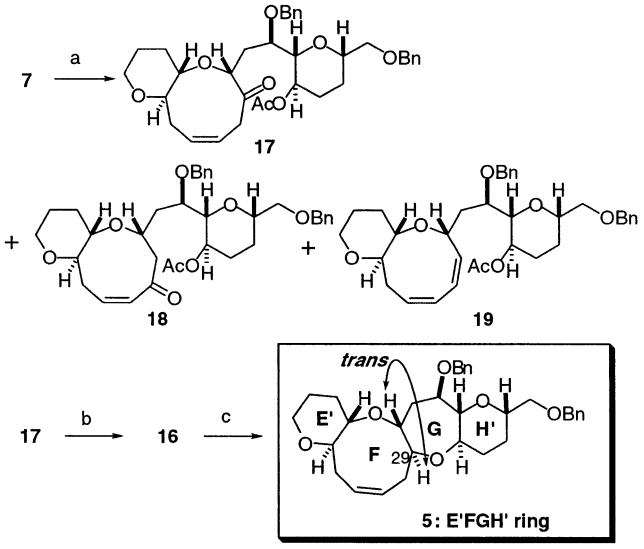


Figure 2 illustrates possible conformational isomers **A**−**D**,[29,30] which were energy-minimized by Macromodel (MM2* force field).[31] Comparison of the coupling constants observed by HOM2DJ (homo *J*-resolved $^1H-^1H$ spectroscopy)[32] of **5** with these of conformers **A**−**D** by Macromodel should predict the majority to exist in similar conformation to DOWN conformer **A** and the minority to exist in similar conformation to UP conformer **B** (Table 1).[33] The orientation of methylene proton at C31

SCHEME 7[a]



[a] G ring cyclization: (a) H_2, 100 kg/cm^2, benzene, 65 °C, 6 h, **17**: 37%, **18**: 4%, **19**: 15%; (b) K_2CO_3, MeOH, 100%; (c) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_3CN, −15 °C to rt, 30 min, 57%.

(28) When measured in Py-d_5 at −20 °C, ^1H NMR spectra of **28** exhibited a 1:1 mixture of two conformational isomers (UP and DOWN conformers).

(29) Three conformers **A**, **B**, and **C** were extracted from results of global search. Conformer **D** was extracted from results of local minimum after flipping the C31 of **B** and corrected for the angle of H29−C29−C30−H30 of **B** as 180°.

(30) The parameters of conformer **A**, **B**, **C**, and **D** are shown in the Supporting Information.

(31) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1900**, *11*, 440.

(32) (a) Aue, W. P.; Karhan, J.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 4226−4227. (b) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon: Oxford, 1991; pp 270−275. (c) Freeman, R. *A Handbook of NMR*; Longman: Harlow, 1987; pp 106−110.

(33) Although reported in ref 18 (our previous paper) that the majority should exist in similar conformation to DOWN conformer **C**, we revise it to DOWN conformer **A** in this paper.

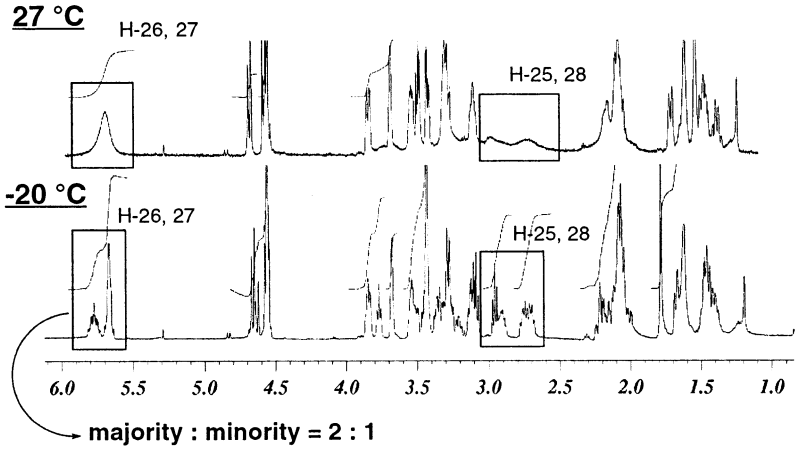


FIGURE 1. ^{1}H NMR spectra (600 MHz) of **5**.

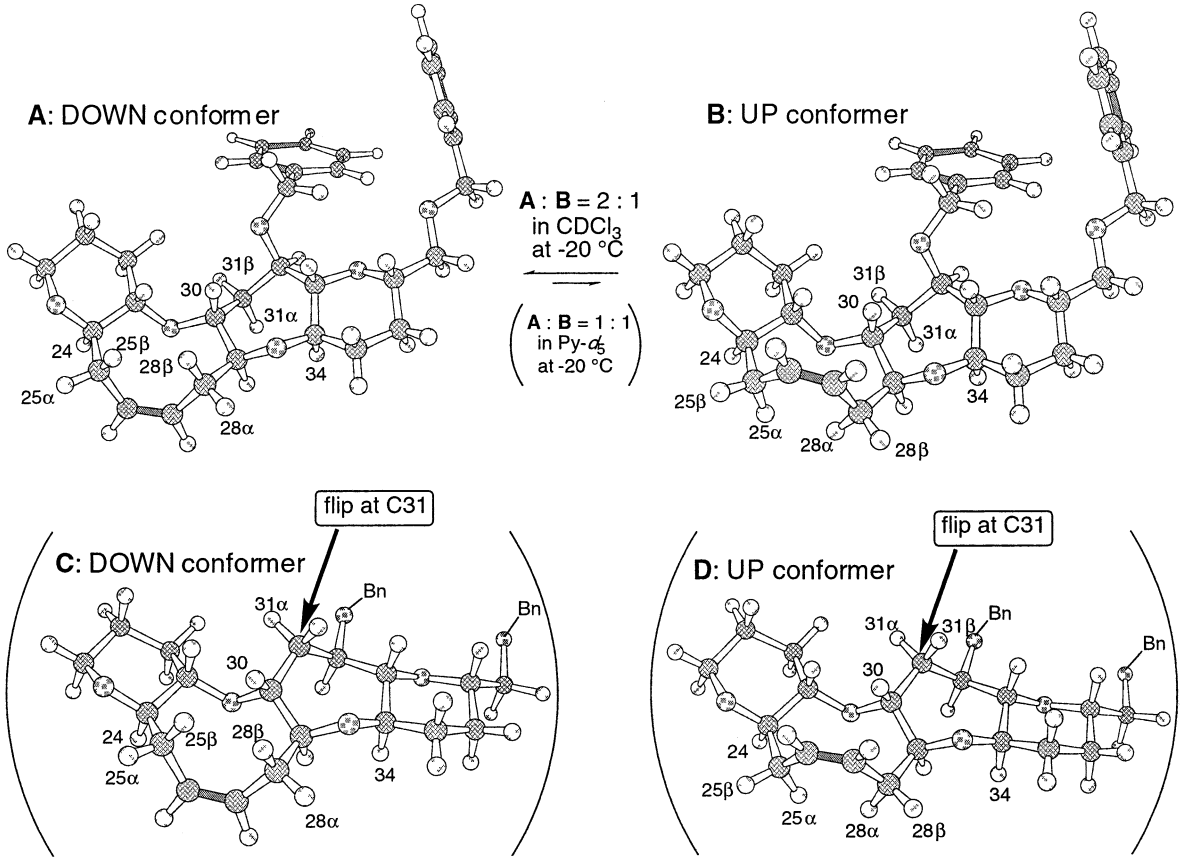


FIGURE 2. Conformational isomers of **5**.

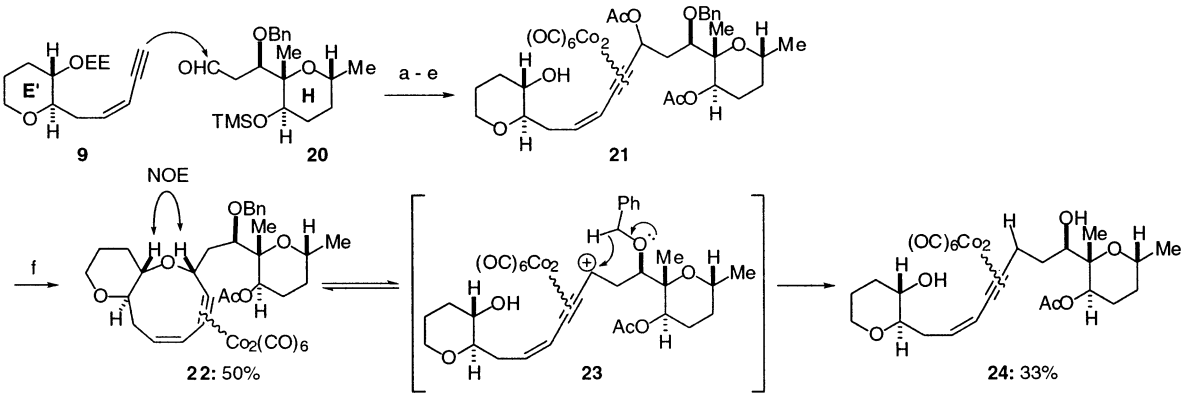
position in conformer **C** (**D**) is just different from that of conformer **A** (**B**).

Although the *syn* stereochemistry between H29 and H34 could not be determined directly by NOE experiments, the fact that the coupling constants between H29 and H30 showed 8.8 Hz for the major conformer and 10.1 Hz for the minor conformer undoubtedly demonstrated the *trans* stereochemistry of **5**.

Having accomplished the convergent synthesis of the E′FGH′ ring fragment **5**, our attention turned to the synthesis of the E′FGH ring fragment **28** having an angular methyl group which exists in natural CTX1B at the G/H ring junction (Schemes 8 and 9). According to the synthesis of **11** as shown in Scheme 3, acetylene cobalt complex **21**, precursor for cyclization, was synthesized from coupling between acetylide of E′ ring-enyne **9** and H ring-aldehyde having an angular methyl group **20** (Scheme 8).[34] In contrast to the synthesis of demethyl analogue **7**, treatment of **21** with BF_3·OEt_2 gave cyclization product **22** and reduction product **24**. Presumably acetylene cobalt complex **22** takes more strained structure than **7** due to the angular methyl group, which triggered ring-opening followed by hydride-transfer from benzyl ether to propargyl cation **23** to afford **24**.[35]

(34) Synthetic scheme and data of **20** are reported in the Supporting Information.

SCHEME 8[a]



[a] Segment coupling and side reaction in the F ring cyclization: (a) **9** (1.5 equiv), *n*-BuLi, THF, −78 °C then **20**, 73% (recovered **20**: 16%); (b) K_2CO_3, MeOH, 95%; (c) Ac_2O, Py, DMAP, CH_2Cl_2, 100%; (d) PPTS, MeOH, 96%; (e) $Co_2(CO)_8$, CH_2Cl_2, 95%; (f) BF_3·OEt_2, CH_2Cl_2, 0 °C, 5 min then rt, 8 min.

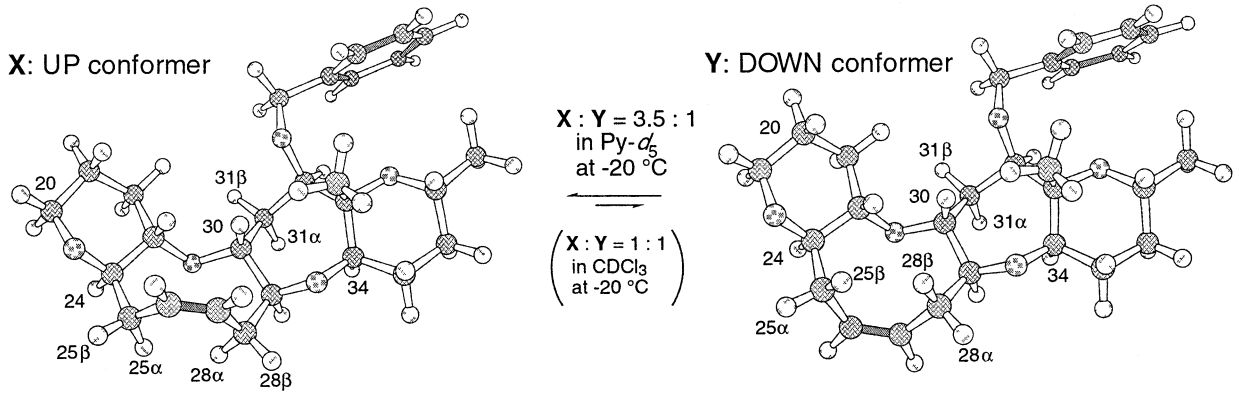


FIGURE 3. Conformational Isomers of **28**.

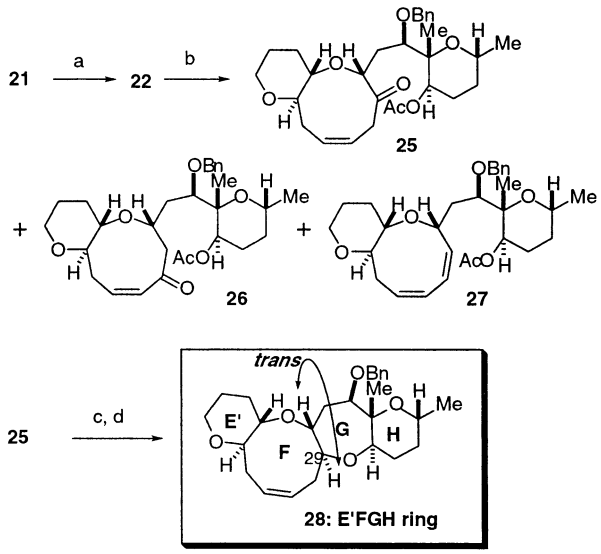
TABLE 1. Comparison of Observed Coupling Constants of 5 with Those of Conformer A−D (in Hz)[a]

^3J	obsd (major)[b]	A	C	obsd (minor)[b]	B	D
24, 25α	ca. 0	2.5	1.4	5.6	5.4	5.4
24, 25*β*	9.9	11.6	10.9	ca. 0	1.7	1.7
28α, 29	1.3	1.9	1.8	5.9	4.3	7.1
28*β*, 29	10.0	11.4	11.3	ca. 0	2.4	1.2
29, 30	8.8	8.6	7.8	10.1	8.5	8.8
30, 31α	8.6	10.8	1.9	13.3	10.5	1.3
30, 31*β*	3.3	1.3	5.2	4.8	1.2	6.8
31α, 32	2.2	3.0	1.4	5.0	3.0	1.6
31*β*, 32	6.5	3.5	11.1	2.5	3.5	11.4
32, 33	4.0	4.9	9.6	2.9	3.5	9.6

[a] The observed coupling constants were obtained from HOM2DJ in $CDCl_3$. On the other hand, the coupling constants of conformers **A**−**D** were obtained by Macromodel. [b] The experimental error was ± 0.2 Hz.

On the other hand, **21** was treated with TsOH·H_2O to give **22** in 86% yield without byproduct **24** (Scheme 9). High-pressure hydrogenation of **22** in hexane gave rise to desired ketone **25** in 46% yield as a major product along with conjugate enone **26** (7%) and diene **27** (12%). Finally, hydroxyketone **25** was successfully transformed into **28** under conditions similar to those of Scheme 7.

SCHEME 9[a]



[a] FG ring cyclization: (a) TsOH·H_2O, CH_2Cl_2, 0 °C to room temperature, 1 h, 86%; (b) H_2, 100 kg/cm^2, hexane, 65 °C, **25**: 46%, **26**: 7%, **27**: 12%; (c) K_2CO_3, MeOH, 97%; (d) BF_3·OEt_2, Et_3SiH, CH_3CN, 72%.

In the ^{1}H NMR analysis of **28** at room temperature, a considerable broadening phenomenon was observed as

(35) (a) Díaz, D.; Martín, V. S. *Org. Lett.* **2000**, *2*, 335−337. (b) Díaz, D.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 743−746. (c) Díaz, D.; Matín, V. S. *J. Org. Chem.* **2000**, *65*, 7896−7901.

TABLE 2. Comparison of Observed Coupling Constants of 28 with These of Conformer X and Y (in Hz)[a]

^3J	obsd (major)[b]	X	Y
24, 25α	5.3	5.5	2.5
24, 25*β*	2.4	1.7	11.6
28α, 29	5.1	4.4	1.9
28*β*, 29	ca. 0	2.4	11.4
29, 30	12.5	8.6	8.6
30, 31α	10.1	10.9	11.1
30, 31*β*	1.0	1.3	1.4
31α, 32	8.2	4.6	4.7
31*β*, 32	5.0	2.3	2.2

[a] The observed coupling constants were obtained from HOM2DJ in Py-d_5. On the other hand, the coupling constants of conformers **X** and **Y** were obtained by Macromodel. [b] The experimental error was ± 0.2 Hz.

the case in E′FGH′ ring **5**.[36] The ^{1}H NMR spectra measured in pyridine-d_5 at −20 °C of **28** exhibited a 3.5:1 mixture of two conformational isomers (UP conformer **X** and DOWN conformer **Y**, Figure 3).[37] Comparison of the coupling constants observed by HOM2DJ with these of conformers **X** and **Y** by Macromodel should predict the majority to exist in similar conformation to UP conformer **X** (Table 2).[38] The trans stereochemistry of **28** should be demonstrated by coupling constants (12.5 Hz) between H29 and H30.

(36) The broadening spectrum was shown in the Supporting Information.

(37) When measured in $CDCl_3$ at −20 °C, the ^{1}H NMR spectra of **28** exhibited a 1:1 mixture of two conformational isomers (UP and DOWN conformers).

(38) The parameters of conformer **X** and **Y** are shown in the Supporting Information.

Conclusion

We have accomplished the convergent synthesis of the central part (E′FGH ring **28** having an angular methyl group) of CTX1B through the coupling reaction between E′ ring-acetylide **9** and H ring-aldehyde **20**, highly stereoselective cyclization of the F ring using an acetylene cobalt complex, and a novel conversion of the complex **22** into ketone **25** followed by reductive hydroxyketone cyclization of the G ring.

In the ^{1}H NMR analysis of **28** at room temperature, a considerable broadening phenomenon was observed due to the slow conformational changes of the FG ring, as reported for natural CTX1B. When measured in pyridine-d_5 at −20 °C, the spectra exhibited a 3.5:1 mixture of two conformational isomers (UP and DOWN conformers). For the conformational assignments of **28**, the experimental methods including HOM2DJ and molecular mechanics calculation methods led us to conclude that the major and minor conformers were assignable to those **X** and **Y**, respectively.

Further studies toward the total synthesis of CTX1B are now in progress.

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Supporting Information Available: Synthetic scheme toward H ring-aldehyde **20**, experimental procedure, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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