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Convergent Synthesis of the Right-Hand Segment of Ciguatoxin

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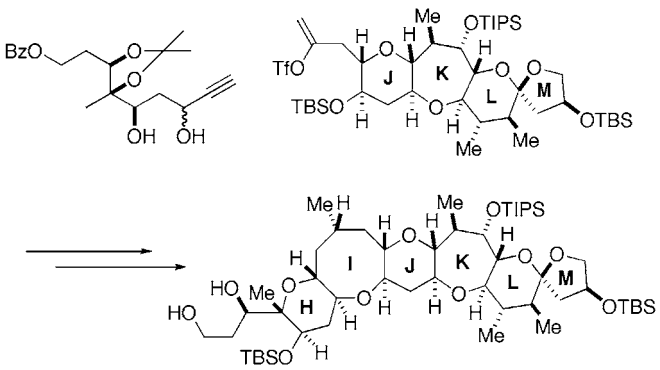
ABSTRACT



A convergent synthesis of the right-hand half of ciguatoxin (the HIJKLM ring system) has been achieved with complete stereocontrol in the introduction of the stereocenters on the eight-membered I ring. Key steps are Sonogashira coupling, dicobalt complexation, intramolecular conjugate addition, and hydrogenation of an *endo*-olefin to provide the 39-α-methyl group.

Ciguatoxin (CTX1B, **1**)[1] is a principal toxin of ciguatera poisoning, which is known as the most widespread seafood problem. Several synthetic groups[2] have been involved in the total synthesis of CTX because of its remarkable structural complexity, biological activity, and limited availability from natural sources. In 2001, the Hirama group reported the first total synthesis of CTX3C, one of the CTX families.[3] We too have been actively pursuing a total synthesis of CTX and have developed several methodologies for constructing its medium-sized ether rings based on cobalt-mediated cyclization.[4]

In our plan for the synthesis of CTX **1**, coupling between an acetylene from the BCDE ring **2** and an aldehyde from the HIJKLM ring **3** is proposed followed by construction of the central FG ring and, finally, A-ring cyclization with the C4 side chain. We have already reported a synthesis of the BCDE ring system **2**[5] and the effective methodologies for construction of the A ring[6] with the side chain. In addition,

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(2) (a) Kobayashi, S.; Takahashi, Y.; Komano, K.; Alizadeh, B. H.; Kawada, Y.; Oishi, T.; Tanaka, S.; Ogasawara, Y.; Sasaki, S.; Hirama, M. *Tetrahedron* **2004**, *60*, 8375−8396. (b) Sasaki, M.; Noguchi, K.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 1425−1428. (c) Takizawa, A.; Fujiwara, K.; Doi, E.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2006**, *47*, 747−751. (d) 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. (e) Bond, S.; Perlmutter, P. *Tetrahedron* **2002**, *58*, 1779−1787. and references therein.

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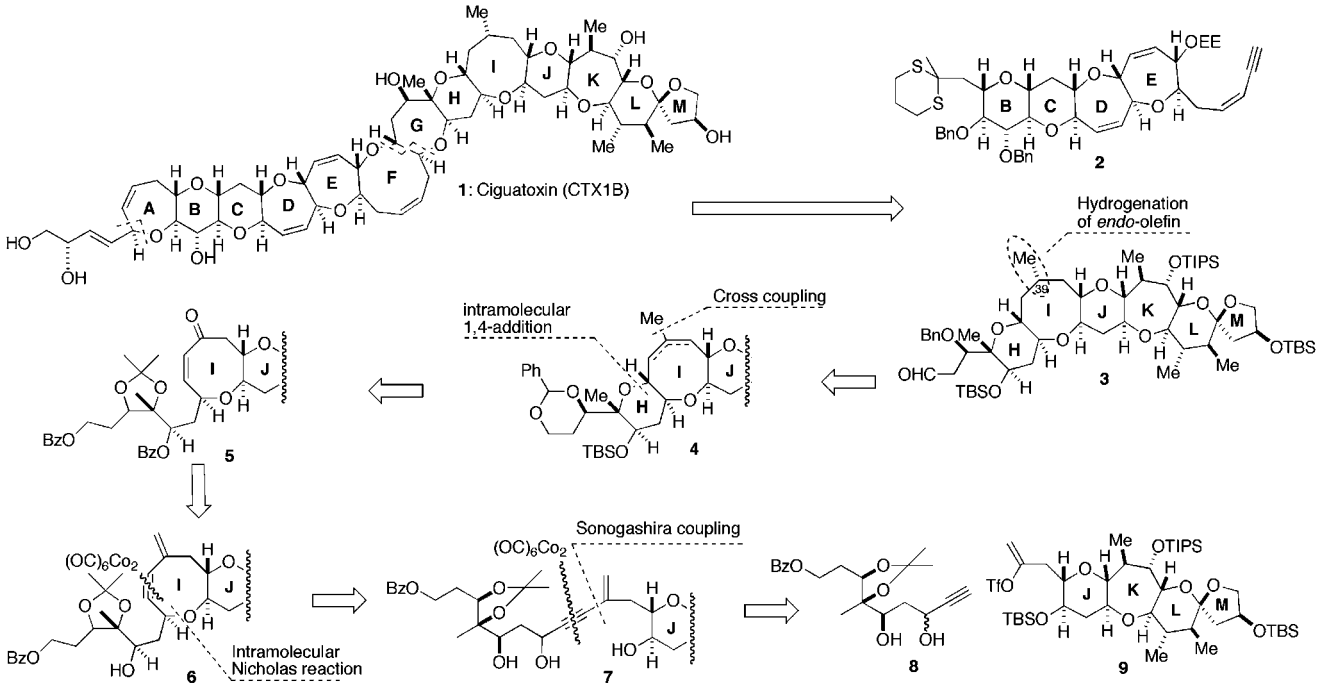
Scheme 1. Retrosynthetic Analysis



the EFGH[7] rings were prepared as model studies for the final stages of the synthesis. On the right-hand part, the syntheses of JKLM[8] and HIJ ring[9] models have already been accomplished. In those model studies, H-ring cyclization was accomplished under strongly acidic conditions, which might ultimately cause problems in our plan because of the fact that the H-ring cyclization step should be achieved in the presence of the acid-labile spiroketal LM ring. Furthermore, introduction of the C(57)-methyl group required six steps. Herein, we report the synthesis of a fully functionalized HIJKLM ring system for ciguatoxin in a shorter number of steps as well as under milder conditions.

Our retrosynthetic analysis of CTX1B **1** is illustrated in Scheme 1. Crucial for introducing the C(57)-methyl group of compound **3** would be the hydrogenation of an *endo*-olefin with the 6-8-6 ether ring system. The *endo*-olefin in **4** has its own stable conformer with its double bond pointing downward as illustrated in Figure 1. Hydrogenation of the double bond would therefore most likely proceed from the β-face to give an α-C(57)-methyl group. The six-membered H ring of **4** would probably be best formed by the intramolecular 1,4-addition of the hydroxyl group in **5**. Its eight-membered ring would be prepared via the acetylene cobalt complex **6**. Opening of the eight-membered ring leads to compound **7**, in which enyne disconnection on the basis of a Sonogashira coupling[10] affords the acetylene **8** and the vinyltriflate **9**.

The vinyltriflate **9** was prepared from **10**[8] in five steps by a series of protecting group manipulations and enolization of methyl ketone **11** with KHMDS and $PhNTf_2$ (Scheme 2).

Construction of the other requisite subsegment **8** required five steps from the diol **12**.[9] The hydroxyl group of **12** was then protected as an acetonide, and the nitrile was reduced in two steps to the alcohol **13** which was protected as a benzoate ester. The acetonide was then selectively deprotected to give subsegment **8**.

Sonogashira coupling between acetylene **8** and vinyltriflate **9** proceeded with high efficiency to furnish the corresponding enyne, from which the TBS groups were removed by treatment with TBAF (Scheme 3). The resulting tetraol **14** could readily be converted into the corresponding acetylene

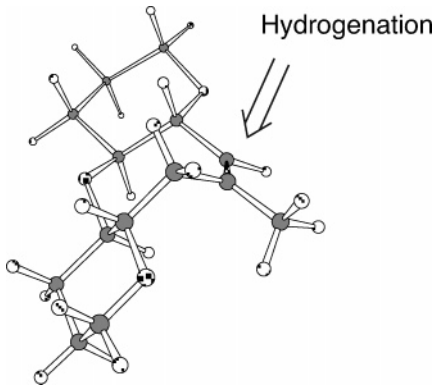


Figure 1. Energy-minimized conformaion of the 6-8-6 ether ring system.

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(8) Baba, T.; Huang, G.; Isobe, M. *Tetrahedron* **2003**, *59*, 6851−6872.
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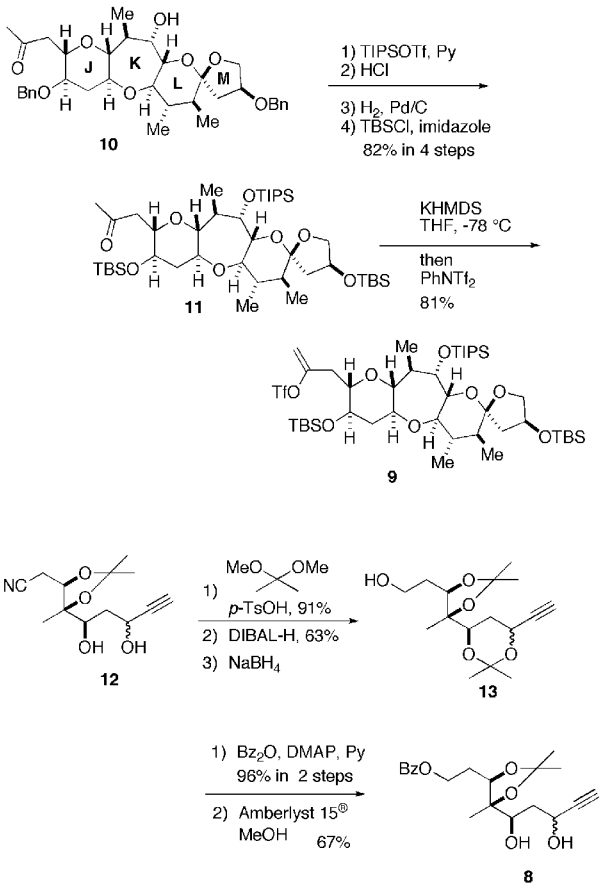
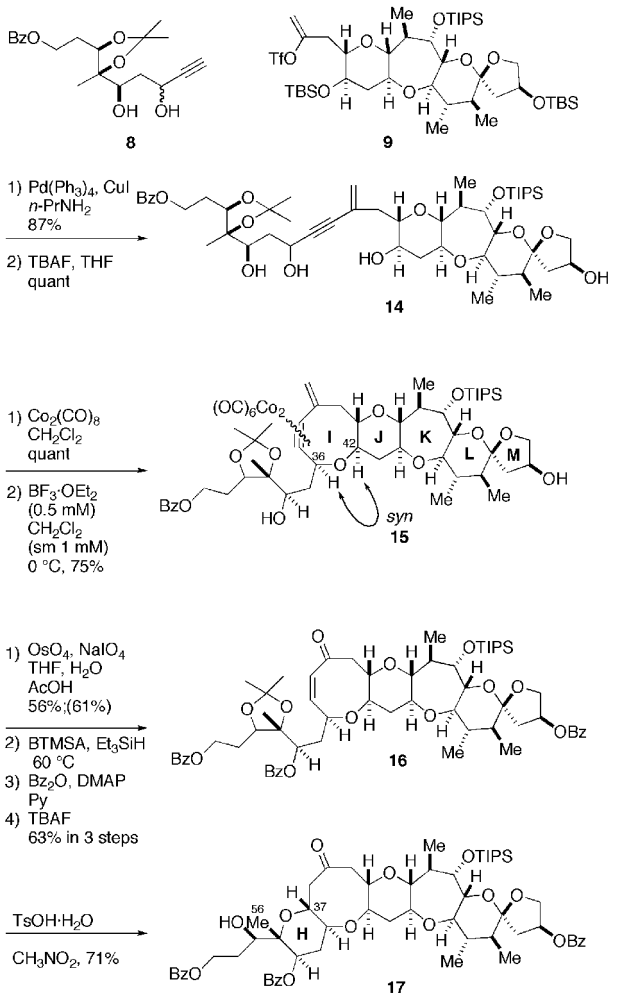
(10) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470.

Scheme 2. Synthesis of Subsegments



Scheme 3. Synthesis of the HIJKLM Ring Fragment



dicobalt complex, which formed by simple mixing with $Co_2(CO)_8$ in CH_2Cl_2. Treatment of this cobalt complex with highly diluted $BF_3{\cdot}OEt_2$ at 0 °C under high dilution conditions resulted in its total consumption within 10 min to afford the pentacyclic system **15** having syn stereochemistry between H(36) and H(42) in 75% isolated yield. At this point, the stereochemistry was exclusively controlled by the thermodynamic stability of the product.

With the requisite IJKLM ring fragment compound **15** in hand, we turned our attention to transforming the cobalt complex of the enyne system to an endocyclic Michael acceptor to form the adjacent six-membered H ring. The exocyclic olefin of **15** was cleaved by Lemieux−Johnson oxidation to afford the corresponding ketone and a mixture of intermediate diols, which was further exposed to $NaIO_4$ to give only the ketone in 61% yield. In this oxidation, the addition of acetic acid did accelerate the oxidative cleavage of the diol and made the reaction reproducible. Hydrosilylation of the acetylene cobalt complex in the presence of bis(trimethylsilyl)acetylene[11] proceeded regioselectively to provide a corresponding vinylsilane. Its two hydroxyl groups were subsequently protected as benzoates, and further treatment with TBAF afforded enone **16**.

Upon treatment of the endocyclic enone **16** with *p*-toluenesulfonic acid in nitromethane, the H-ring cyclization took place with attendant loss of the acetonide group to afford the target hexacyclic compound **17** having syn stereochemistry between the C(56)-methyl and H(37) as a major product. Through inspection of the stability of the spiroketal under acidic conditions, it was found that the benzoyl-protected spiroketal was more stable under acidic conditions than when it was protected as a benzyl ether or left unprotected. In this regard, when the spiroketal protected with *O*-benzyl groups was exposed to the same acidic conditions, it decomposed rapidly.

The only issue that remained was stereoselective introduction of the methyl group at the C(39) position (Scheme 4). After the benzoyl group of **17** was removed, the 1,3-diol containing primary alcohol was protected as an *O*-benzylidene acetal. The remaining hydroxyl groups were protected as TBS ether. The ketone present in the I ring was converted into a vinyl triflate; the C(39)−(40) double-bond isomer was the major product. The vinyl triflate was cross-coupled with methylmagnesium bromide in the presence of

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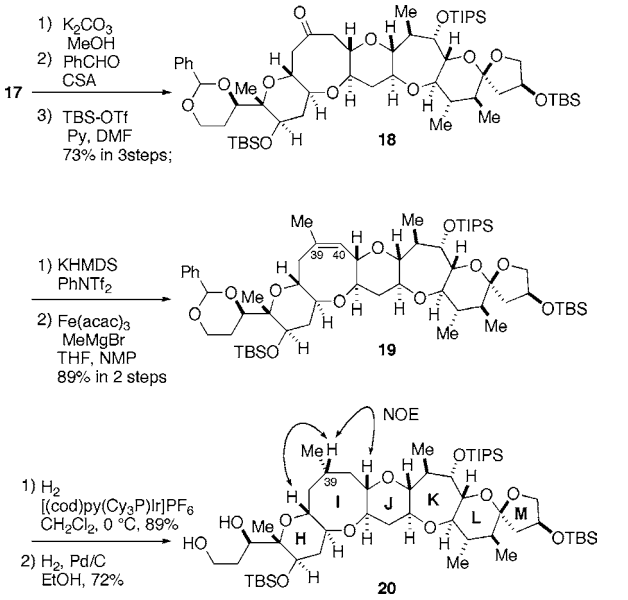
Scheme 4. Introduction of the 57-Methyl Group



$Fe(acac)_3$, affording the *endo*-olefin **19** in good yield.[12] The *endo*-olefin was hydrogenated stereoselectively using Crabtree's catalyst to give a single diastereoisomer.[13] We could not determine the stereochemistry of the C(39) position in this step. Fortunately, we found that the 600 MHz ^{1}H NMR spectrum of deprotected diol **20** in pyridine-d_5 showed good resolution in the upfield region. NOE correlation and the ^{1}H NMR coupling constant determined the stereochemistry of the C(39) position to be α.

In conclusion, we have accomplished a synthesis of a fully functionalized HIJKLM ring fragment. The key transformations in our synthesis are I-ring cyclization using the acetylene cobalt complex, the intramolecular 1,4-hydroxy addition under mild acidic conditions, and stereoselective hydrogenation of the I ring *endo*-olefin. Further studies toward the total synthesis of ciguatoxin are now in progress.

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

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