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Natural Product Synthesis

Total Synthesis of Ciguatoxin**

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Ciguatoxin (CTX1B; **1**) is one of the main toxins involved in ciguatera poisoning.[1] Its structure was elucidated by Yasumoto and co-workers, and has a ladder-shaped *syn,trans*-fused polycyclic ring system that includes 33 stereogenic centers.[2] As a result of their limited availability and interesting structural features, ciguatoxins have been the target of several synthetic studies.[3] In 2006, Hirama and co-workers reported the first total synthesis of **1**.[4a] Our research group has independently explored various new methodologies toward the total synthesis of **1**.[5] One of our main concepts is a strategy that involves the use of a acetylene–dicobalthexacarbonyl complex, which mediates coupling reactions and the cyclization of ether rings of different sizes (seven-, eight-, and nine-membered rings). The cyclization strategy was designed so that preorganization is effected by the bulky ligands and cation stabilization is induced by the Nicholas effect[6] under acidic conditions.[7] This type of cyclization is, in fact, always stereoselective and gives *syn,trans* products having endocyclic acetylene–dicobalthexacarbonyl complexes, which can be further transformed under reductive decomplexation conditions into either *cis* olefins or vinylsilanes.[8] These acetylene–dicobalthexacarbonyl complexes were found to convert into ketones under oxidative decomplexation conditions.[9] Also, our method is more reproducible and reliable when the ligand is bidentate. Advances in this transformation have allowed us to achieve the total synthesis of **1**, which is described herein.

With this cyclization strategy at hand, as well as our syntheses of both enantiomers of the ABC ring (with the side chain),[10] BCDE ring,[11] EFGH ring,[12] HIJ ring,[13] JKLM ring,[14] and HIJKLM ring,[15] we developed a sequence to complete the total synthesis of ciguatoxin (**1**; Scheme 1). In our retrosynthetic analysis, **1** would be disconnected between C5 and C6 to give terminal acetylene **2** and aldehyde **3**. Owing to the acid-labile nature of the doubly allylic ether at C5, it was decided that the A ring should be formed at the latest possible stage in the synthesis. We had also decided to use an alternative acid-labile spiroacetal at C52. Further disconnection of **2** would occur between C29 and C30 to give a terminal acetylene **5** (left-hand segment) and aldehyde **6** (right-hand segment).

The acetylene group in **2** could be prepared from a methyl ketone through a vinyl triflate obtained from the corresponding secondary alcohol, which can be protected as the 2-naphthylmethyl (NAP) ether. Compound **4**, which can be derived from the coupling product between **5** and **6**, could be first cyclized to form the F ring according to the acetylene–dicobalthexacarbonyl strategy. In turn, this complex can be converted into a ketone at C29, which whould allow cyclization to give the F ring. Formation of the G ring could be promoted through a cyclic acetal **2** (X = OMe). The requisite conversion of the cobalt complex of **4** into a ketone at C29 could be achieved through a regioselective oxidative decomplexation.

The left-hand segment consisting of the BCDE ring **5** was synthesized in essentially the same manner as outlined in our previous report.[11] Meanwhile, the right-hand segment consisting of the HIJKLM ring **6** was synthesized in two steps from our previously reported benzylidene acetal derivative.[15] Reaction between the lithium acetylide of **5** and aldehyde **6** afforded an inseparable mixture, which included the four diastereomeric propargyl alcohols as well as starting material **5** and unchanged **6** (48%) (Scheme 2). After further treatment with TBAF, the mixture was separated by silica gel column chromatography and afforded triol **7** (54% yield in 2 steps from **5**) as a mixture of diastereomers and unchanged **5** (25%). The hydroxy groups of **7** were protected as acetates, and subsequent removal of the ethoxyethyl group with an acidic resin gave propargyl acetate **8** (*m*/*z* 1761.91). The acetylenic moiety of **8** was converted into the corresponding acetylene–dicobalthexacarbonyl complex, which was cyclized by treatment with *p*-toluenesulfonic acid (TsOH) and yielded the nine-membered ring **9** in 72% yield as a single stereoisomer. The protons at C23 and C30 of the newly formed ring junction showed an NOE interaction to support the *syn* configuration. Oxidative decomplexation was best achieved regioselectively in one pot; first by heating with bis(diphenylphosphino)methane (dppm) to replace two of the six carbonyl ligands, and subsequent introduction of air to obtain the ketone **10**.[16] Removal of the acetyl groups was followed by treatment with trimethylorthoformate in the presence of CSA in nitromethane/methanol (10:1), and afforded the seven-membered cyclic methylacetal **11** (X = OMe) in 80% yield in two steps. This product was further treated with triethylsilane in the presence of borontrifluoride diethyletherate and gave the reduced compound, which represented the BCDEFGHIJKLM ring system **11** (X = H) in 60% yield. The ^{1}H NMR spectrum was compared with the reported data[2b] to confirm the configuration around the F and G rings of **11**. In this ^{1}H NMR analysis, a considerable broadening of the signals was observed resulting from the

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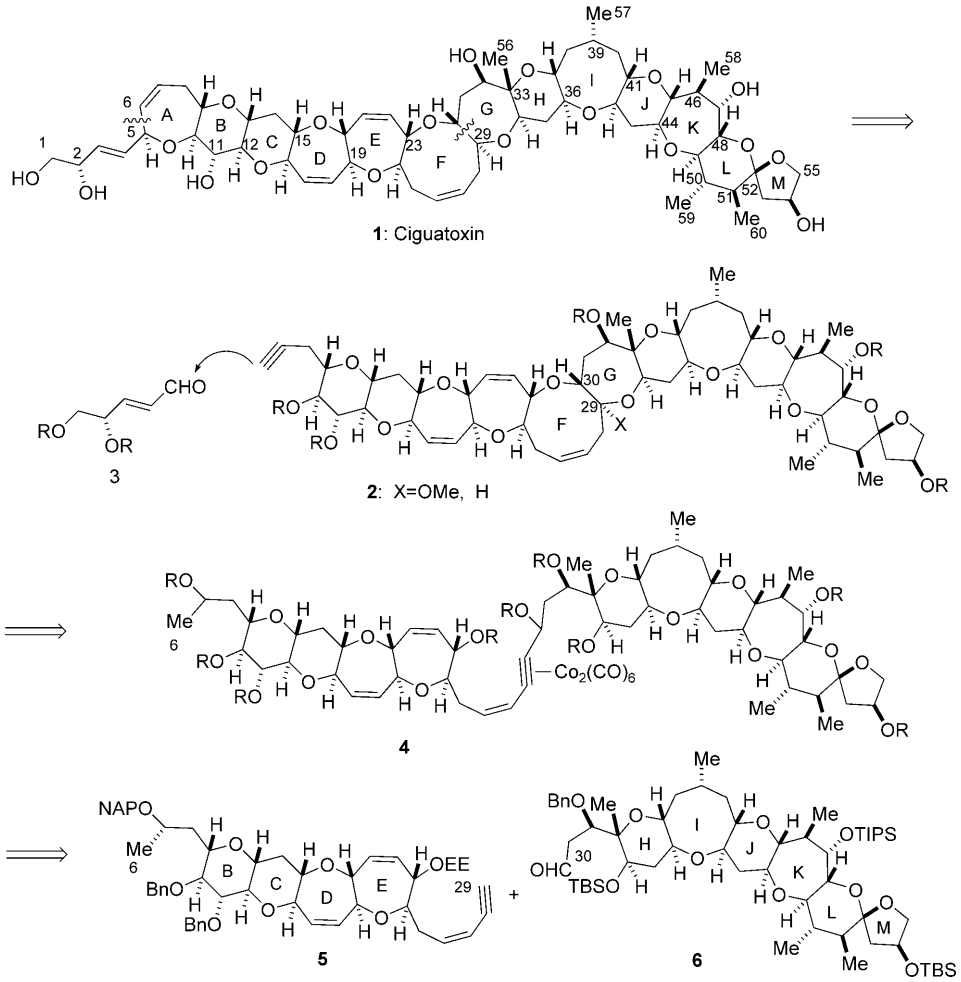


Scheme 1. Retrosynthetic analysis of ciguatoxin (CTX1B; **1**). Coupling of the segments and cyclization of medium-sized ether rings through acetylene–dicobalthexacarbonyl complexation. Bn = benzyl, EE = ethoxyethyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

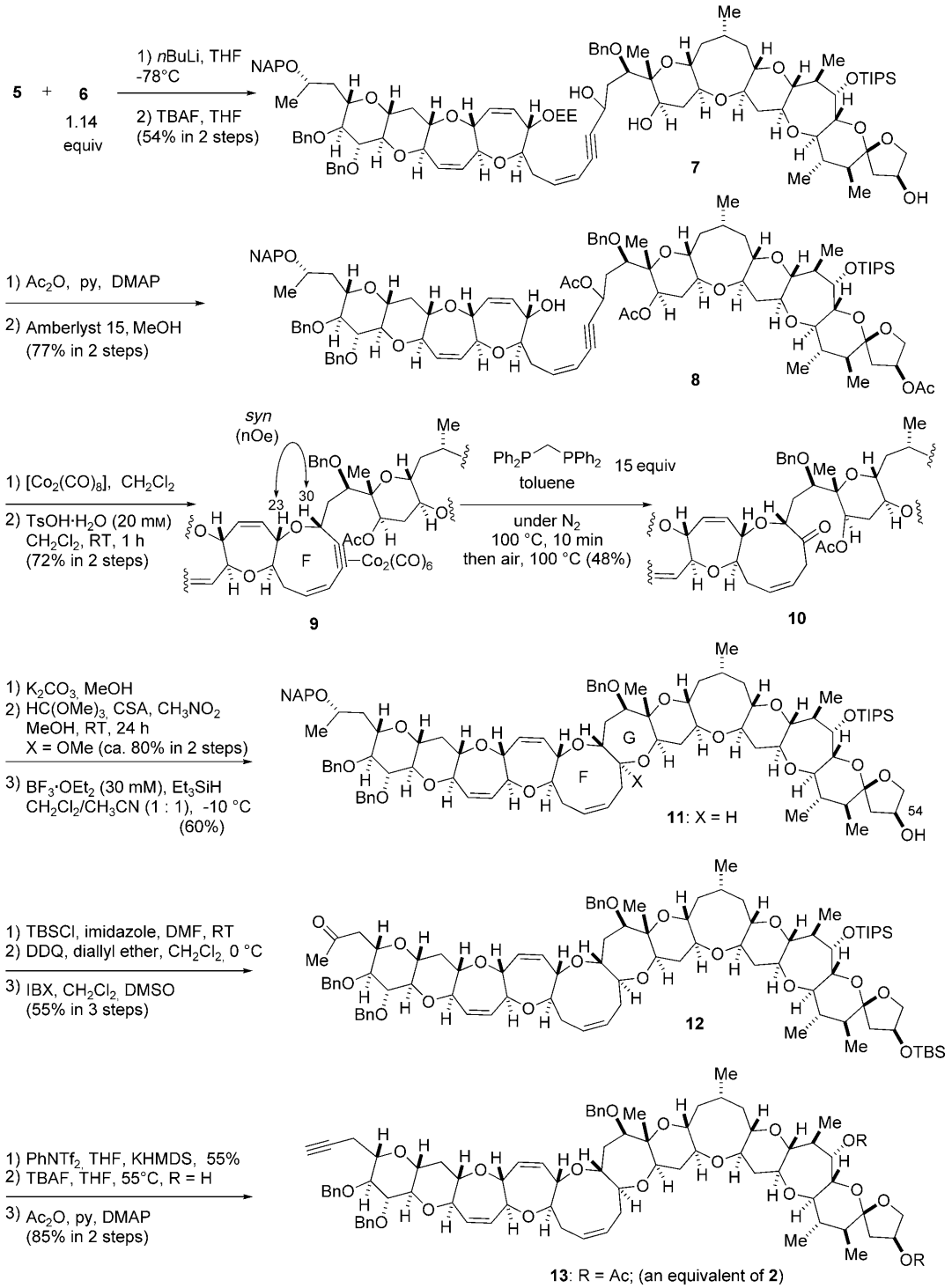
slow conformational changes of the F ring—this phenomenon has also been reported for ciguatoxin (CTX1B) and the E′FGH-ring model compound.[12]

Protection of the hydroxy group at C54 as a TBS ether, and subsequent removal of the NAP group with DDQ did not effect the three benzyl groups in **11**. The resultant secondary alcohol was oxidized with IBX and afforded the methylketone **12**. Conversion of **12** into the corresponding vinyltriflate was achieved in a regioselective manner in the presence of *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$) and KHMDS. Further elimination of the resultant vinyltriflate moiety was carried out with TBAF and provided the acetylene group with concomitant cleavage of two silyl ethers, and the subsequent acetylation gave **13** (R = Ac).

The final coupling reaction to give the A ring and the side chain proved to be problematic when the lithium acetylide of **13** (R = TIPS or TBS) and aldehyde **3** were mixed in THF. This complication was in contrast to the positive outcome obtained for smaller model compounds, which provided propargylic adducts in high yield and that were further converted into the A ring with the side chain.[17] Thus, anionic coupling was abandoned owing to the difficult reactivity of the carbanion in polyethereal compounds, and we were therefore obliged to change the envisioned synthesis. It was now hoped that the terminal acetylene **13** (R = Ac) would couple with vinyliodide **17**, and then cyclize to give the A ring upon double-bond migration. Compound **17**, which had the 2*R* configuration, was prepared from D-glycelaldehyde **14** in six steps (Scheme 3). Thus, treatment with nBuLi and trimethylsilylacetylene gave propargyl alcohol **15**, and subsequent protective-group manipulation gave tripivaloyl acetylene **16**, which was subjected to hydrostannation and finally iodination to afford *trans* vinyliodide **17**.

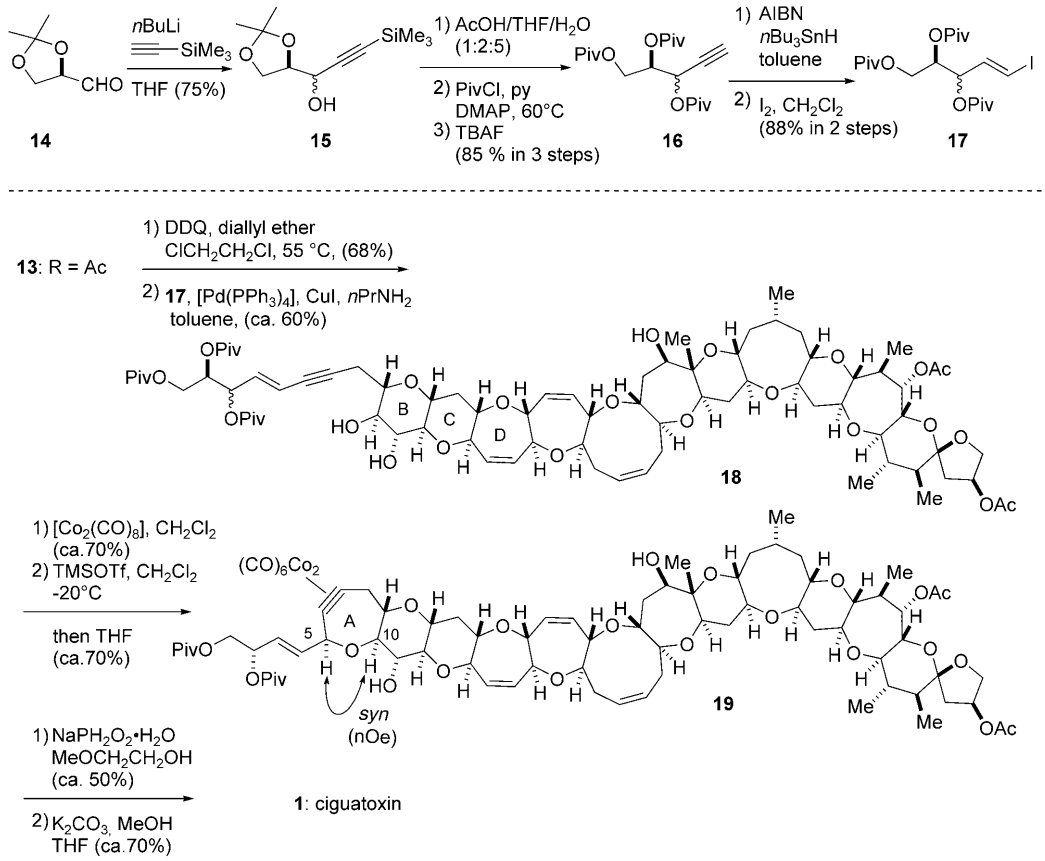
The three benzyl groups of **13** (R = Ac) were cleaved with DDQ, and the product was then isolated as the corresponding triol, which was subjected to Sonogashira coupling with vinyliodide **17** and furnished enyne **18** (Scheme 3). Compound **18** was treated with $[Co_2(CO)_8]$ to obtain the corresponding acetylene–dicobalthexacarbonyl complex. Further treatment with excess TMSOTf at −20 °C generated a stable propargyl cation in dichloromethane. Under such highly acidic conditions, the A ring existed largely in equilibrium with its open form. The addition of THF at −20 °C was used to scavenge the excess Lewis acid and therefore shifted the equilibrium toward the cyclization product **19**.[18] The NOE interaction between H5 and H10 of **19** allowed confirmation of its *syn* configuration. Reductive decomplexation of the *endo* complex **19** was accomplished with excess sodium hypophosphite in 2-methoxyethanol and provided a *cis* olefin. Final removal of the four acyl groups with K_2CO_3 in methanol/THF (1:1) afforded ciguatoxin (**1**). Purification of this final product was achieved by using reversed phase column chromatography. The ^1H NMR and MS data of the pure sample were identical to those for the naturally derived material.[2b,4]

In summary, we have successfully completed the total synthesis of ciguatoxin through the coupling of three segments mediated by our acetylene–dicobalthexacarbonyl strategy. After coupling of two big segments (the BCDE and HIJKLM rings previously synthesized by us), the F ring



Scheme 2. Coupling the acetylene **5** (left-hand) and aldehyde **6** (right-hand) segments to form the F and G rings, and synthesis of the terminal acetylene. CSA = 10-camphorsulfonic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, IBX = *o*-iodoxybenzoic acid, py = pyridine, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

was cyclized using the acetylene–dicobalthexacarbonyl strategy. The resulting complex was oxidized to give a ketone at C29, which led to the subsequent formation of the G ring in a stereoselective manner. Final coupling to the *trans* vinyliodide segments allowed the formation of the A ring with the side chain, again through the acetylene–dicobalthexacarbonyl strategy. The total synthesis was completed in 22 steps where the average yield for each step was 73%.



Scheme 3. The total synthesis of ciguatoxin (CTX1B; **1**) through formation of the A ring by coupling, cyclization to give the seven-membered ring, and double-bond migration. AIBN = 2,2′-azobisisobutyronitrile, Piv = pivaloyl.

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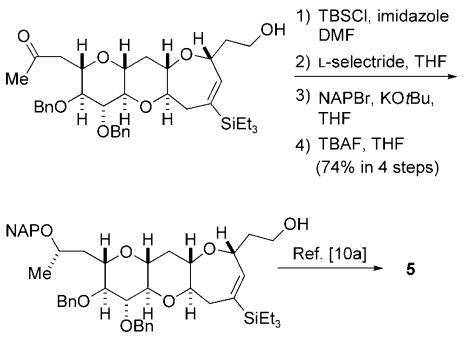

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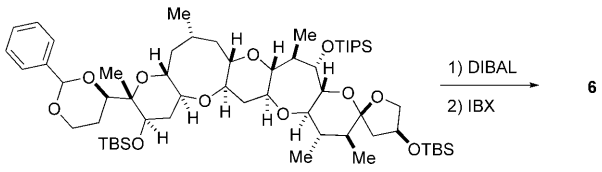

[16] The critical oxidation of the acetylene–dicobalthexacarbonyl complexes that gave ketones was not highly reproducible (10–40% yield) when heated in the form of the hexacarbonyl ligand (see Ref. [12]). Among various bidentate ligands examined, we found that the dppm ligand gave the best reproducibility with model compounds (40–75% yield; see Ref. [9]).

[17] This complication may result from the formation of a cluster between the anionic species and the polyether moieties in the molecule. This situation may be similar to a previous problematic case that we reported during the total synthesis of okadaic acid, a marine polyether, in the coupling between a sulfonyl carbanion and an aldehyde. In this case, changing the solvent from pure THF to Et_2O/*n*-hexane (3:2) resulted in dramatic reaction progress; however, this type of salt/solvent system was not successful for coupling in ciguatoxin; see: M. Isobe, Y. Ichikawa, D.-L. Bai, H. Masaki, T. Goto, *Tetrahedron*, **1987**, *43*, 4767 – 4776..

[18] After the eneyne coupling, the acetylene was converted into the dicobalthexacarbonyl complex **19a**, which was subjected to cyclization under acidic condition. The initial intermediate—where the allylic cation is located at C3—might be stabilized by the neighboring pivaloyl group at C2, and became reactive as intermediate **19b** by the addition of THF solvent.