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Construction of the C46-C55 Fragment of Ciguatoxin

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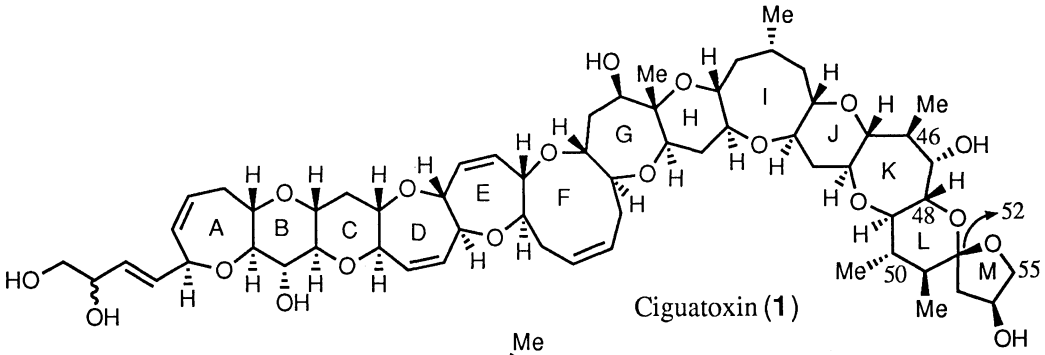
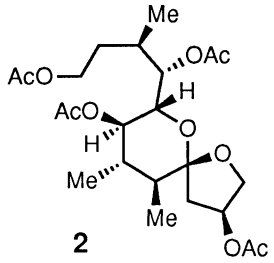
The compound with all the necessary functional groups of the KLM ring system in ciguatoxin, which is one of the most complicated toxic substances of marine origin, was synthesized stereoselectively. The crucial steps involve construction of the ethynyl alcohol, the δ-valerolactone, and the natural acetals.

The structure of ciguatoxin (**1**), isolated as the principal toxin causing ciguatera from the moray eal *Gymnothorax javanicus*, has been elucidated by Yasumoto and Murata,[1] and its characteristic polycyclic system including 13 medium sized cyclic ethers seems to be one of the most challenging synthetic target molecules. Very recently, Tachibana et al. has reported the first construction of the KLM ring system of **1**.[2] Their publication has prompted us to submit our own results on the the corresponding ring moiety. We describe herein the synthesis of **2** including all the correct chiral centers in rather short steps.[3]

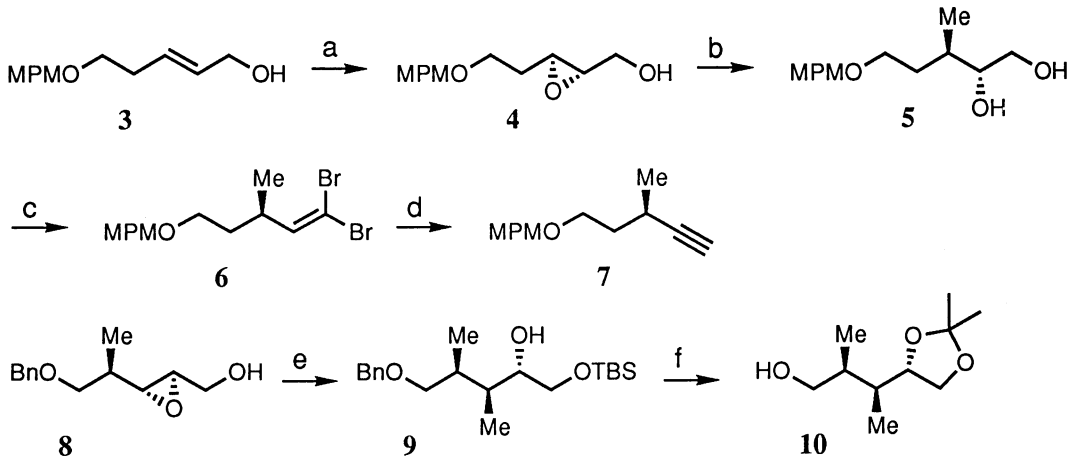


Ciguatoxin (**1**)



2

Our synthesis has commenced from the preparation of **7** and **10** starting from **3**[4] and **8**,[5] respectively (Scheme 1). Compound **3** was oxidized under the Sharpless conditions using L-(+)-DET to afford the epoxy alcohol **4** (95% ee), which gave rise to the methylated *vic*-diol **5** with Me_3Al.[6] The diol part was cleaved and the product was treated immediately with CBr_4 and PPh_3 to yield the dibromo-olefin **6**. The compound was converted smoothly with BuLi to the alkyne **7**. On the other hand, compound **8** (>95% ee) was treated also with Me_3Al[6] to give the *vic*-dimethyl, *vic*-diol **9**, which was transformed into the acetonide alcohol **10**.

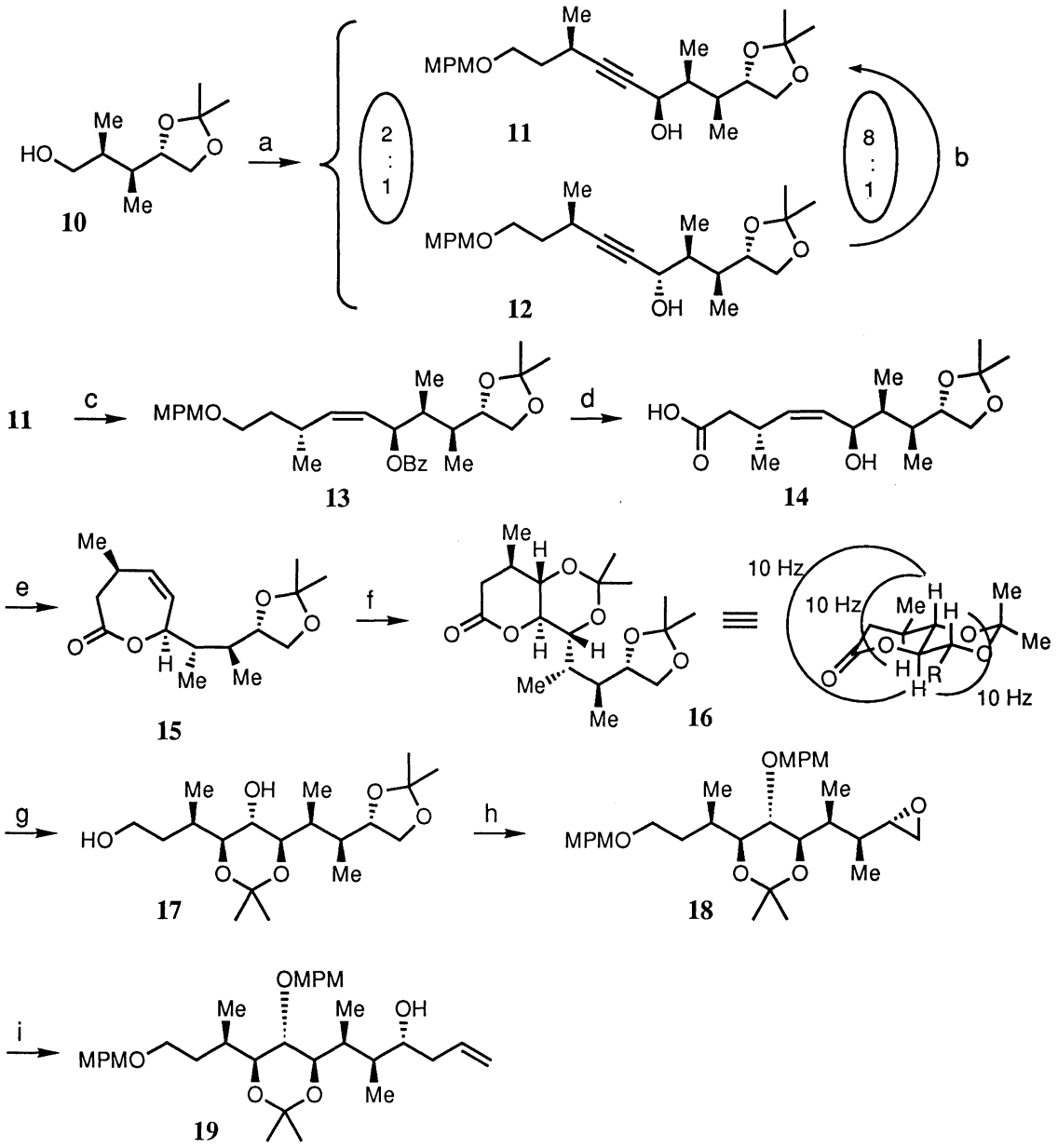


a) L-(+)-DET, $Ti(OPr^i)_4$, TBHP, MS4A, CH_2Cl_2, -20 °C, 20 h, 94%; b) Me_3Al, Hex-CH_2Cl_2 (2:1), 0 °C → 20 °C, 16 h, 77%; c) $NaIO_4$, THF-H_2O (1:1), 20 °C, 10 min; CBr_4, PPh_3, CH_2Cl_2, 0 °C, 20 min, 97%; d) BuLi, THF, -78 °C, 30 min, 87%; e) Me_3Al, Hex-CH_2Cl_2 (2:1), 0 °C → 20 °C, 17 h, 95%; TBSCl, NEt_3, DMAP, CH_2Cl_2, 20 °C, 17 h, 66%; f) acetone, PTS, 20 °C, 36 h, 93%; H_2, 10% Pd/C, EtOH, 20 °C, 24 h, 98%.

Scheme 1.

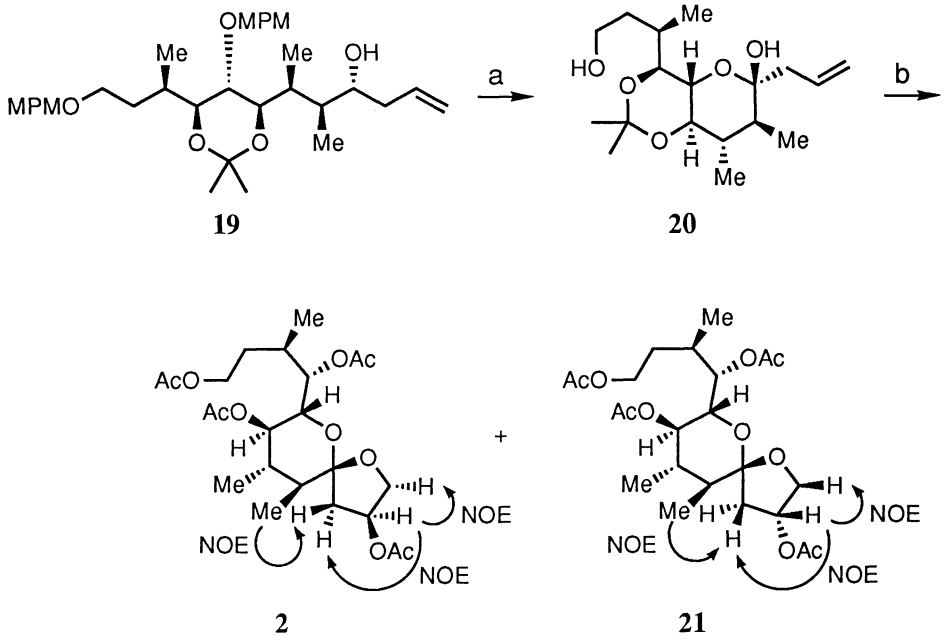
Compound **10** was oxidized under the Swern condition and immediately allowed to react with a soln of **7** and BuLi (Scheme 2). A coupling reaction proceeded smoothly to afford a 2:1 mixture of acetylene alcohols (**11** and **12**). The stereochemistry of the introduced hydroxyl group was deduced by applying the improved Moscher procedure[7] to both the MTPA esters of **11**. While the fact that compound **11** was preferable had been expected on the basis of the Cram rule,[8] the relative ratio of **11** to **12** was rather low. Then, the compounds were oxidized with PDC and then reduced with some agents. DIBAH reduction in CH_2Cl_2 at -78 °C for 10 min afforded a 1:2 mixture (78%) of **11** and **12**. Reaction with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in EtOH at 20 °C for 20 min produced a 4:1 mixture (86%) of **11** and **12**. Finally, reduction with $LiAlH(OBu^t)_3$ in ether at 0 °C for 3 h yielded a 8:1 mixture (83%) of **11** and **12**. The desired compound **11** was then hydrogenated with Lindlar catalyst and esterified to give the *cis*-olefin benzoate **13**, which was converted into the hydroxy carboxylic acid **14** in a three step process. Compound **14** was cyclized internally to the lactone **15** in a high yield by the Yamaguchi procedure.[9] Successive treatment of the lactone **15** with OsO_4 (1 eq), H_2S, and acetone and conc HCl gave rise to compound **16** exclusively in a good yield.[10] Compound **16** was reduced with $LiAlH_4$ to **17**, which was converted under the usual conditions to the epoxide **18**. Then, the epoxide was smoothly transformed into the allyl alcohol **19**.

Compound **19** was treated with AD-mix α[11] in *t*-BuOH-H_2O (1:1) at 0 °C → 20 °C for 24 h followed by acetonization to yield the corresponding undesired (2*R*)-triol acetonide (46%), along with a mixture of the desired (2*S*)-triol acetonides (27%). On the other hand, the compound **19** was oxidized under the Swern condition and deprotected with DDQ to afford the acetal **20** in a high yield (Scheme 3).[12] Treatment of compound **20** with OsO_4 (1 eq), TFA, and Ac_2O produced the desired internal acetal **2** and its epimer **21** in 22 and 15% overall yields from **20**, respectively.[13] The compound **2** obtained thus constitutes the C46-C55 fragment of ciguatoxin with all the necessary funtional groups. Further synthetic studies on the other ring fractions directing toward the total synthesis of **1** are now in progress.



a) Swern oxid.; **7**, BuLi, THF, -78 °C, 30 min; aldehyde, -78 °C, 1 h, 88%; b) PDC oxid.; $LiAlH(OBu^t)_3$, ether, 0 °C, 3 h, 83%; c) H_2, Lindlar cat., MeOH, 20 °C, 2 d, 98%; BzCl, NEt_3, DMAP, CH_2Cl_2, 20 °C, 15 h, 100%; d) DDQ, CH_2Cl_2-H_2O (10:1), 0 °C, 1.5 h, 63%; PDC oxid., 90%; $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (4:1), 0 °C, 1.5 h; 1M KOH, aq. MeOH, 20 °C, 24 h, 75%; e) 2,4,6-trichlorobenzoyl chloride, NEt_3, toluene, 20 °C, 18 h; DMAP, toluene, 20 °C, 1 h, 81%; f) OsO_4, THF-Py (4:1), 20 °C, 2 h; H_2S, MeOH, 20 °C, 1 h; acetone, conc HCl, 20 °C, 3 h, 67%; g) $LiAlH_4$, ether, 0 °C → 20 °C, 1.5 h, 92%; h) MPMCl, KH, TBAI, THF, reflux, 4 h, 95%; 1M HCl, aq MeOH, 20 °C, 3 h, 75%; 2,4,6-triisopropylbenzenesulfonyl chloride, NEt_3, DMAP, CH_2Cl_2, 20 °C, 26 h, 87%; K_2CO_3, MeOH, 20 °C, 2.5 h, 100%; i) Li acetylide-EDA, DMSO, 20 °C, 4 h, 81%; H_2, Lindlar cat., PhH, 20 °C, 30 min, 100%.

Scheme 2.



a) Swern oxid.; DDQ, CH_2Cl_2-H_2O (10:1), 20 °C, 1.5 h, 92%; b) OsO_4, MeCN-H_2O (2:1), 20 °C, 1 h; TFA, CH_2Cl_2, 20 °C, 1 h; Ac_2O, DMAP, Py, 20 °C, 3 h, **2**, 22%, **21**, 15%.

Scheme 3.

References

1) M. Murata, A. M. Legrand, Y. Ishibashi, M. Fukui, and T. Yasumoto, *J. Am. Chem. Soc.*, **112**, 4380 (1990).
2) M. Sasaki, M. Inoue, and K. Tachibana, *J. Org. Chem.*, **59**, 715 (1994).
3) This research was presented in the preliminary form at the 67th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1994.
4) Compound **3** was prepared in 4 steps in 54% overall yield starting from propane-1,3-diol.
5) Compound **8** was prepared in 12 steps in 18% overall yield starting from (2*Z*)-butene-1,4-diol according to the Kishi procedure on the enatioisomer of **8**; cf., H. Nagaoka and Y. Kishi, *Tetrahedron*, **37**, 3873 (1981).
6) T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **23**, 3597 (1982); W. R. Roush, M. A. Adam, and S. M. Peseckis, *ibid.*, **24**, 1377 (1983).
7) I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, **113**, 4092 (1991).
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9) J. Inagawa, K. Hirata, S. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
10) The stereochemistry of the *vic*-diol introduced was determined by the respective coupling constants (10 Hz each) between the four successive protons in ^{1}H-NMR spectrum of **16** (cf., Scheme 2). For prediction of the stereochemistry in major osmylation products of allylic alcohol systems, see J. K. Cha, W. J. Christ, and Y. Kishi, *Tetrahedron*, **40**, 2247 (1984).
11) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, **57**, 2768 (1992).
12) Reaction of **20** with AD-mix α in *t*-BuOH-H_2O (1:1) at 0 °C → 20 °C for 48 h gave a complex mixture.
13) The stereochemistry of **2** and **21** was deduced from the NOE experiments, respectively (cf., Scheme 3).

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