Synthetic Studies toward Ciguatoxin. Stereocontrolled Construction of the KLM Ring Fragment

Makoto Sasaki, Masayuki Inoue, and Kazuo Tachibana*

Department of Chemistry, School of Science, The University of Tokyo, Bunkyo-ku, Tokyo 113, Japan

Received November 15, 1993®

Summary: The first stereoselective synthesis of the KLM ring fragment of ciguatoxin is reported including as a key step 7-endo selective cyclization of epoxy alcohol to construct a fully substituted oxepane ring (**12** → **13**).

Ciguatoxin (**1**) and its congeners are the toxic principles of ciguatera, which is known as the most widespread among sea food poisonings of dinoflagellate origin (Figure 1).[1] The toxin molecule **1** is one of the most potent neurotoxins and binds to the same site of voltage-dependent sodium channels as structurally similar brevetoxins.[2] However, its very limited availability from natural sources has prevented further studies including precise conformational analysis, characterization of the interaction with sodium channels, and development of a highly specific immunoassay for its detection in food sources. Thus, its synthetic supply is urgently needed.[3] In this paper, we report the first stereoselective synthesis of the KLM ring fragment of this molecule, which appears to be well-suited for a haptenic epitope of anti-ciguatoxin antibody.[4] The present synthesis is based on the 7-endo selective cyclization of the epoxy alcohol as a key step for the efficient construction of the fully substituted oxepane ring K.

The synthesis of the KLM ring fragment started with methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-altropyranoside (**2**),[5,6] whose configurations at C2–C5 correspond to those at C46–C49 of ciguatoxin, respectively. The alcohol **2** was transformed into nitrile **3** in 68% overall yield by the following sequence (Scheme 1): (1) benzylation, (2) acid hydrolysis of the benzylidene group, (3) selective tosylation of the primary hydroxyl, and (4) treatment with sodium cyanide in DMSO. DIBALH reduction of **3** followed by $NaClO_2$ oxidation led to the hydroxy carboxylic acid, which was treated with phenylsulfonyl chloride and triethylamine to give the *trans*-fused bicyclic lactone **4** in 51% overall yield from **3**. Introduction of the α-oriented methyl group at the C50 position[7] was realized with complete stereocontrol by a two-step sequence of reactions [(1) LDA, THF, −78 °C; MeI; (2) LDA, THF, −78 °C; saturated aqueous NH_4Cl] in 76% yield. Dithiane alcohol **6**, obtained by treatment of **5** with 1,3-propanedithiol (TMSOTf, CH_2Cl_2, 0 °C, 96%), was converted to its TBDMS ether **7** in quantitative yield. Cleavage of the dithiane **7** with 5 equiv of *N*-iodosuccinimide (NIS) in aqueous acetonitrile[8] and subsequent Horner–Emmons olefination gave the α,β-unsaturated ester **8** in 92% overall yield. Katsuki–Sharpless asymmetric epoxidation[9] of allylic alcohol **9**, prepared from **8** by a three-step protocol (74% overall), was followed by protection of the primary alcohol to afford MOM ether **10** in high yield. DIBALH reduction of the lactone **10** and protection of the resulting hemiacetal according to the method of Sinou[10] provided allyl ether **11** as a 3:2 anomeric mixture in 91% overall yield. After removal of the TBDMS group (94%), treatment of epoxy alcohol **12** with dimsylpotassium (THF, rt, 3 h) resulted in the predominant formation of fully substituted oxepane **13** accompanied by tetrahydropyran **14** in 80% total yield. In this cyclization, 7-endo cyclization proceeded preferentially in spite of the absence of an activator group such as an electron-rich olefin for the selective cleavage of the epoxide.[11] The presence of the *trans*-fused five-membered ring is presumed to be responsible for the observed selectivity, although the extent of its contribution is unclear.[12] Difference in the regioselectivity of the cyclization was observed between the two diastereomers, i.e., the 51β allyl ether **12β**[13] provided only the desired oxepane **13β**, whereas the 51α allyl ether **12α**[13] produced an inseparable 1.7:1 mixture of oxepane **13α** and tetrahydropyran **14**.

In order to construct the L ring, we needed one-carbon homologation for **13** (Scheme 2). Thus, protection of the hydroxyl group of the mixture of **13** and **14** as the TIPS

® Abstract published in *Advance ACS Abstracts*, February 1, 1994.

(1) (a) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380. (b) Lewis, R. J.; Sellin, M.; Poli, M. A.; Norton, R. S.; MacLeod, J. K.; Sheil, M. M. *Toxicon* **1991**, *29*, 1115. (c) Murata, M.; Legrand, A.-M.; Scheuer, P. J.; Yasumoto, T. *Tetrahedron Lett.* **1992**, *33*, 525. (d) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975. (e) Lewis, R. J.; Norton, R. S.; Brereton, I. M.; Eccles, C. D. *Toxicon* **1993**, *31*, 637.

(2) Gawley, R. E.; Rein, K. S.; Kinoshita, M.; Baden, D. G. *Toxicon* **1992**, *30*, 780 and references cited therein.

(3) For other synthetic works, see: (a) Alvarez, E.; Díaz, M. T.; Pérez, R.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2241. (b) Alvarez, E.; Zurita, D.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2245. (c) Zárraga, M.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2249. (d) Alvarez, E.; Rodríguez, M. L.; Zurita, D.; Martín, J. D. *Tetrahedron Lett.* **1991**, *32*, 2253. (e) Suzuki, T.; Sato, O.; Hirama, M.; Yamamoto, Y.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron Lett.* **1991**, *32*, 4505. (f) Sato, O.; Hirama, M. *Synlett* **1992**, 705. (g) Alvarez, E.; Rico, M.; Rodríguez, R. M.; Zurita, D.; Martín, J. D. *Tetrahedron Lett.* **1992**, *33*, 3385. (h) Ravelo, J. L.; Regueiro, A.; Martín, J. D. *Tetrahedron Lett.* **1992**, *33*, 3389. (i) Soler, M. A.; Palazón, J. M.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5471.

(4) Hokama, Y.; Hong, T. W. P.; Isobe, M.; Ichikawa, Y.; Yasumoto, T. *J. Clin. Lab. Anal.* **1992**, *6*, 54.

(5) Hicks, D. R.; Fraser-Reid, B. *Can. J. Chem.* **1975**, *53*, 2017.

(6) The absolute stereochemistry of ciguatoxin was proposed to be one represented by structure 1; see ref 3e.

(7) The numbering of compounds used in this paper corresponds to that of ciguatoxin (Figure 1).

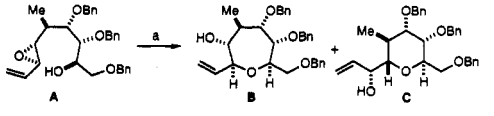
(8) A variety of reagents were tested for the oxidative hydrolysis of dithiane in **7**, among which 5 equiv of NIS in aqueous acetonitrile at room temperature was found to be the best set of conditions with respect to the yield and its reproducibility.

(9) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.

(10) Lakhmiri, R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1989**, *30*, 4669.

(11) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.

(12) Base treatment of epoxy alcohol **A** gave a mixture of oxepane **B** and tetrahydropyran **C** in 27% and 57% yield, respectively.

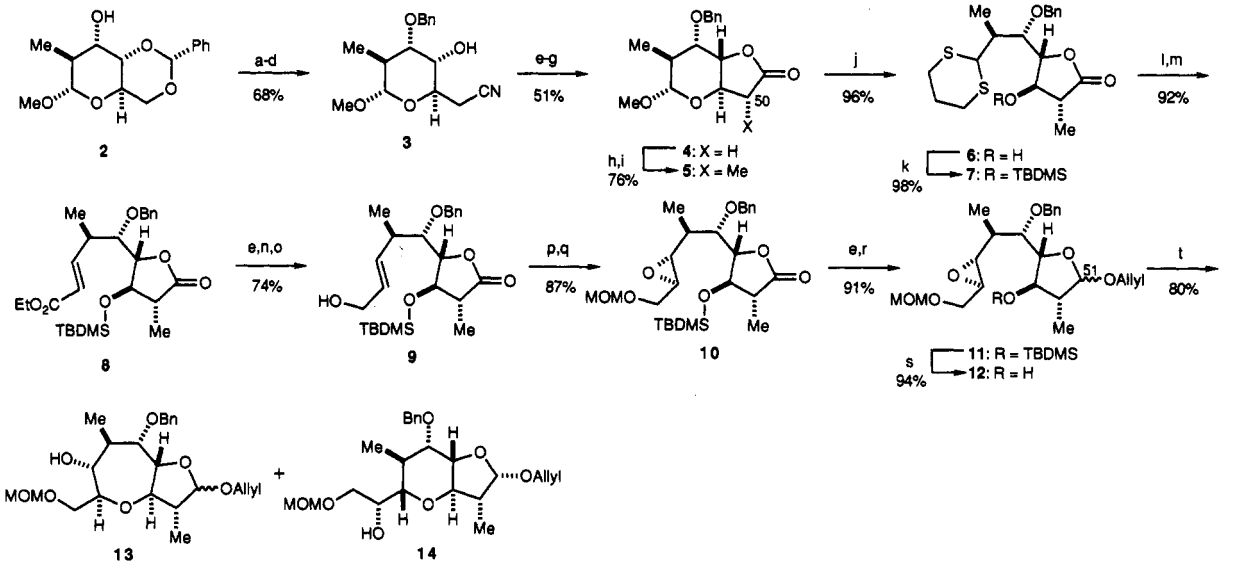


(a) KCH_2SOCH_3, DMSO, rt

(13) A part of the 3:2 mixture of **12α** and **12β** was separated by HPLC (YMC A024 SIL column, 10 × 300 mm; eluent, 25% ethyl acetate in hexane; UV 254 nm; flow rate, 3.0 mL/min; t_R, **12α**, 23.6 min; **12β**, 24.7 min).

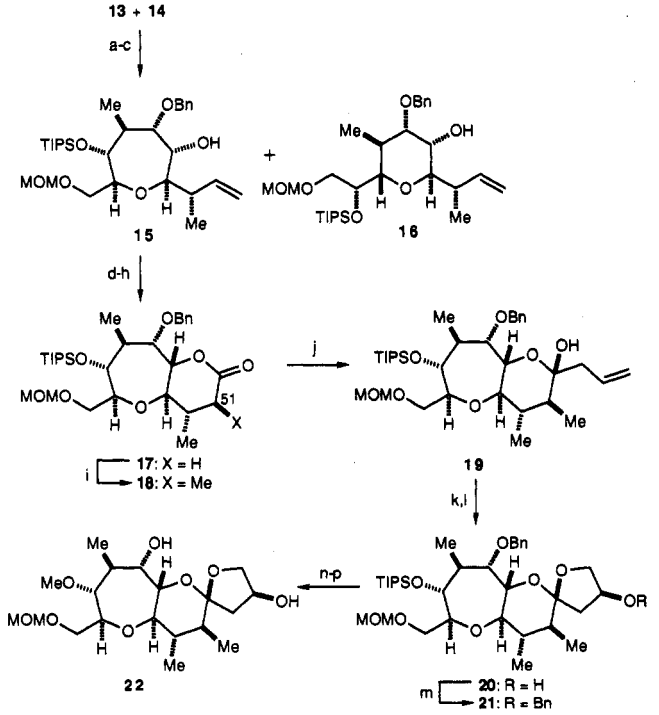
0022-3263/94/1959-0715$04.50/0

Scheme 1[a]



[a] Key: (a) NaH, BnBr, DMF, rt; (b) TsOH, MeOH, rt; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (d) NaCN, DMSO, 70 °C; (e) DIBAL, CH_2Cl_2, −78 °C; (f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–H_2O, rt; (g) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to rt; (h) LDA, MeI, THF, −78 °C; (i) LDA, NH_4Cl, THF, −78 °C; (j) $HS(CH_2)_3SH$, TMSOTf, CH_2Cl_2, 0 °C; (k) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt; (l) NIS, CH_3CN–H_2O, rt; (m) $(i\text{-PrO})_2POCH_2CO_2Et$, KO*t*-Bu, THF, −78 to 0 °C; (n) PDC, 4 Å MS, CH_2Cl_2, rt; (o) $NaBH_4$, MeOH, 0 °C; (p) *t*-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$, (−)-diethyl tartarate, CH_2Cl_2, −20 °C; (q) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt; (r) allylOCO_2Et, Pd_2(dibenzylideneacetone)$_3$·$CHCl_3$, 1,4-bis(diphenylphosphino)butane, THF, 65 °C; (s) *n*-Bu_4NF, THF, rt; (t) KCH_2SOCH_3, THF, rt.

Scheme 2[a]



[a] Key: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt; (b) $PdCl_2$, NaOAc, AcOH–H_2O, rt, 74% (two steps); (c) $Ph_3P^+CH_3Br^-$, KHMDS, THF, 0 °C, **15**: 64%, **16**: 24%; (d) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 86%; (e) 9-BBN, THF, rt; H_2O_2, NaOH, rt, 91%; (f) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (g) AcOH–THF–H_2O (3:3:1), rt; (h) PDC, 4 Å MS, CH_2Cl_2, rt, 83% (three steps); (i) LDA, MeI, THF–HMPA, −78 °C, 52% (77% based on the recovered starting material); (j) AllylMgBr, THF, −78 °C, 79%; (k) OsO_4, *N,N'*-bis(2,4,6-trimethylbenzyl)-(*S,S*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, −90 °C; aq $NaHSO_3$–THF, reflux, 78%; (l) CSA, PhH, rt, 97%; (m) NaH, BnBr, DMF, 0 °C to rt, 90%; (n) *n*-Bu_4NF, THF, rt, 98%; (o) KH, MeI, THF, 0 °C to rt, 94%; (p) H_2, 20% $Pd(OH)_2$/C, EtOH, rt, 67%.

ethers and selective removal of the allyl group with $PdCl_2$ under mild conditions[14] (74% overall yield) followed by Wittig olefination provided hydroxy olefins **15** (64%) and **16** (24%). At this stage, the undesired tetrahydropyran **16** was easily removed by silica gel chromatography. Conventional functional group manipulation allowed for the transformation of the pure oxepane **15** to the *trans*-fused lactone **17** in five steps: [(1) triethylsilylation (86%); (2) hydroboration using 9-BBN (91%); (3) oxidation with SO_3·Pyr; (4) selective hydrolysis of the triethylsilyl group to form the corresponding hemiacetal; (5) PDC oxidation (83% for the three steps)]. Methylation of the lithium enolate derived from **17** led exclusively to **18** with the desired configuration at the C51 position in 52% yield (77% based on the recovered starting material) and subsequent introduction of the allyl group as a three-carbon unit for the construction of the spirally attached M ring furnished the hemiketal **19** in 79% yield. Application of the asymmetric osmylation with *N,N'*-bis(2,4,6-trimethylbenzyl)-(*S,S*)-1,2-diphenyl-1,2-diaminoethane[15] gave the triol (78%), which upon treatment with camphorsulfonic acid (PhH, rt) gave rise to the spiroketal **20** in 97% yield. Finally, benzylation of the hydroxyl group at C54 gave the protected KLM ring fragment **21** in 91% yield. The stereochemistry at the C52 and C54 positions were assigned on the basis of literature precedent,[15] differential NOE experiments, and our preceding model study.[16] Compound **21** was converted into **22** by the following sequence in 61% overall yield: (1) *n*-Bu_4NF, THF, rt; (2) KH, MeI, THF, 0 °C to rt; (3) H_2, 20% $Pd(OH)_2$/C, EtOH, rt. Its ^1H NMR spectrum in pyridine-d_5 matched well with that of ciguatoxin.

The synthesis reported herein has the potential to provide adequate amounts of a structural fragment of ciguatoxin for further research, including its use as a hapten

(14) Nakada, T.; Kitajima, T.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1992**, *228*, 157.
(15) Corey, E. J.; Jardine, D. P.; Virgil, S.; Yuen, P.-W.; Connel, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.
(16) Sasaki, M.; Hasegawa, A.; Tachibana, K. *Tetrahedron Lett.* **1993**, *34*, 8489.

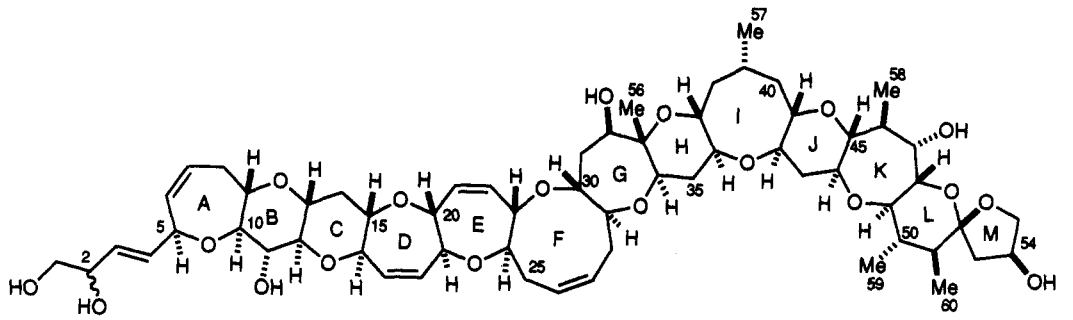


Figure 1. Structure and the ring assignment of ciguatoxin (1).

of antigens to raise monoclonal antibodies that could recognize the natural toxin. Further studies toward this direction are currently underway.

Acknowledgment. We thank Prof. Michio Murata of this department for valuable discussions and advice throughout this work.

Supplementary Material Available: Experimental procedures and spectroscopic data for compounds **3-22** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm addition of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.