# Diastereoselective Synthesis of the GH Ring Part of Ciguatoxin

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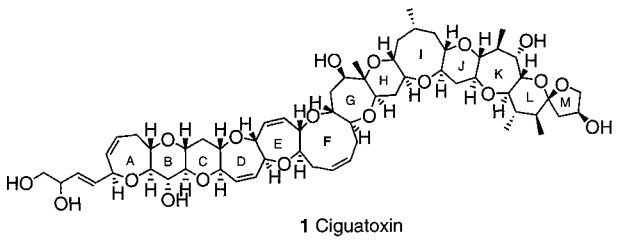
**Abstract**: Substrate-controlled stereoselective synthesis of the GH ring part of ciguatoxin **1** was achieved.

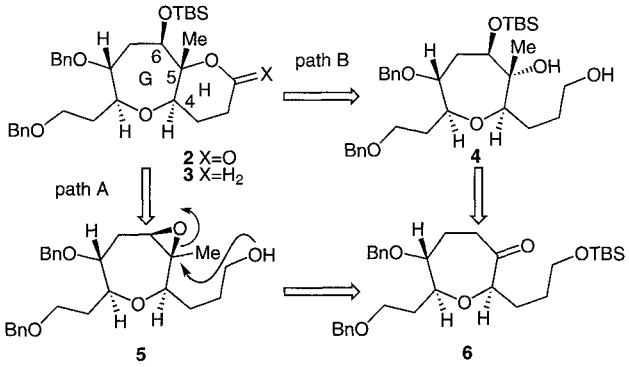
Ciguatoxin **1** has been isolated as a food poisoning principle of ciguatera from the moray eel *Gymnothorax javanicus*.[1] The compound, which was structurally determined by T. Yasumoto *et al.* in 1989,[2] is one of the most attractive synthetic target molecules,[3] because of its strongly toxic activity and novel polycyclic ethereal structure. We describe here the construction of the racemic GH ring fragments **2** and **3** as a part of our total synthetic study on **1**.



1 Ciguatoxin

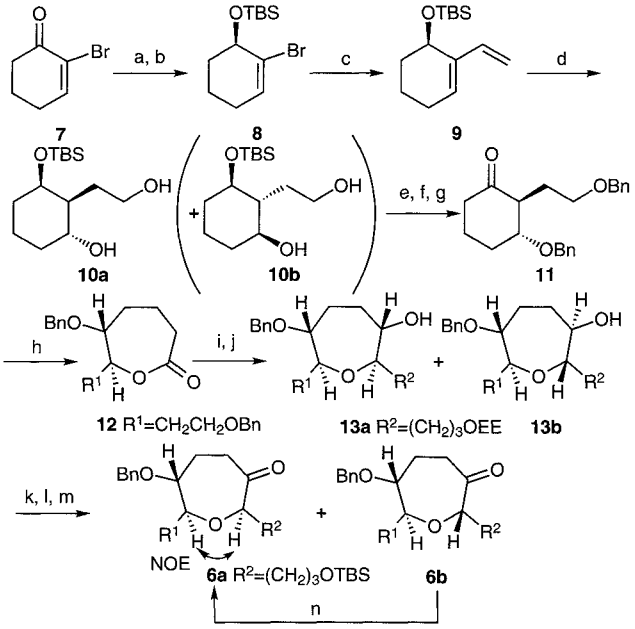
**Figure 1**

Retrosynthetic analyses of **2** and **3** are shown in Scheme 1. The syntheses involved two problems; one was the stereoselective construction of C5 and C6 asymmetric centers in **4** and **5**, and the other was establishment of the cyclization method of the H ring. We thought that the former problem could be solved by help of the character of the 7-membered ring ether. Concerning the latter problem, we proposed two paths: i) simultaneous cyclization with construction of asymmetric centers at C5 and C6 (path A); ii) cyclization after introduction of all functionalities (path B).



**Scheme 1**

Synthesis of the oxepane ring compound **6** was started from 2-bromo-2-cyclohexen-1-one **7**[4] (Scheme 2). Compound **7** was converted to silyl ether **8** by 1,2-reduction and silylation. Treatment of **8** with vinylmagnesium bromide and a catalytic amount of $Pd(PPh_3)_4$ in THF at 60 °C produced diene **9**,[5] which was transformed into diols **10a** and **10b** as a 3:1 mixture by hydroboration and oxidation. Ketone **11** was prepared from the major diol **10a** by a 3 step-conversion: protection with BnBr, removal of the TBS group, and oxidation of the alcohol. Also, the minor diol **10b** was converted to **11** in 6 steps.[6] Baeyer-Villiger oxidation of **11** produced lactone **12**. Treatment of **12** with KHMDS and $PhNTf_2$ followed by reaction with organocuprate in one pot[7] gave a cyclic enol ether, which was led to **13a** and **13b** as a 3:1 mixture by hydroboration and oxidation. The protecting group of the mixture was exchanged to TBS ether, which was oxidized to a separable mixture of ketones **6a** and **6b** in 63% and 23% yields from **13**, respectively. The undesired ketone **6b** could be isomerised with DBU in toluene at 60 °C to the desired **6a**. The stereochemistry of **6a** and **6b** was determined by the differential NOE experiment of **6a**.

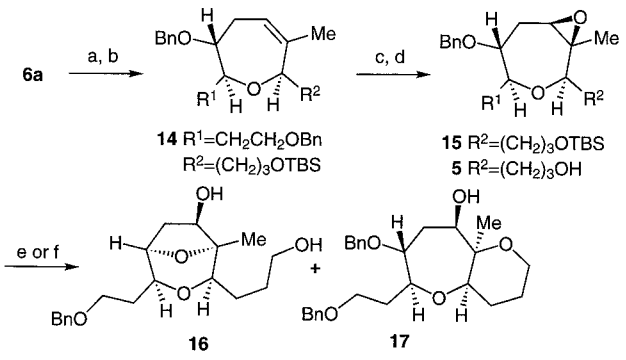


(a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, r.t., 10 min., 90%; (b) TBSCl, imidazole, DMF, r.t., 9 h, ~100%; (c) vinylmagnesium bromide, $Pd(PPh_3)_4$ (cat.), THF, 60 °C, 2 h, 89%; (d) i) $(Sia)_2BH$, THF, 0°C, 2 h; ii) $BH_3{\cdot}THF$, 0 °C to r.t., 2 h; iii) NaOH aq., $H_2O_2$, r.t., 8 h, 77% (**10a**:**10b**=3:1); (e) BnBr,*t*-BuOK, TBAI, THF, 0 °C, 1 h, 94%; (f) 1M HCl in $H_2O$-MeOH (1:20), r.t., 6 h, ~100%; (g) i) $(COCl)_2$, DMSO, $CH_2Cl_2$, -50 °C, 2 h; ii) $Et_3N$, 0 °C, 20 min., 97%; (h) *m*CPBA, $NaHCO_3$, dichloroethane, 60 °C, 6 h, 85%; (i) i) KHMDS, HMPA, THF/toluene, -78 °C, 2 h; ii) $PhNTf_2$, -78 °C, 2 h ; iii) $[EEO(CH_2)_3]_2Cu{\cdot}MgBr$, THF, -78 °C, 1 h; (j) i) $BH_3{\cdot}THF$, THF, 0 °C, 2 h; ii) NaOH aq., $H_2O_2$, 60% (from **12**), (**13a**:**13b**=3:1); (k) 1M HCl in $H_2O$-THF (1:10), r.t., 8 h, ~100%; (l) TBSCl, $Et_3N$, DMAP, $CH_2Cl_2$, r.t., 3.5 h, 95%; (m) Swern oxid., -78 °C, 2 h, 91%; **6a**: 63% (from **13**); **6b**: 23% (from **13**); (n) DBU, toluene, 60 °C, 3 days, 94%.

**Scheme 2**

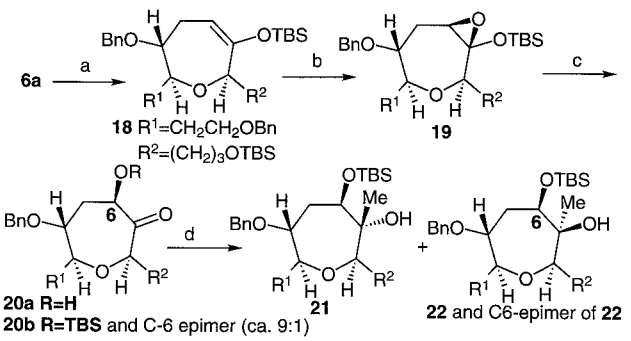
At first, we attempted the cyclization of the H ring *via* path A (Scheme 3). Treatment of **6a** with LiHMDS and $PhNTf_2$ produced a single regioisomer of the enol triflate, which was converted to olefin **14** by coupling reaction with $Me_2CuLi$. Epoxidation of **14** with *m*CPBA in the presence of $NaHCO_3$ in $CH_2Cl_2$ at 0 °C gave the desired epoxide **15**[8] in 89% yield and a small amount of the diastereomer (7% yield). Epoxy alcohol **5** was prepared by deprotection of **15** with TBAF in THF. When **5** was treated with a catalytic amount of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at room temperature, bicyclo compound **16** and *cis*-fused ether **17** as an isomer of **3**, were produced in 32% and 5% yield, respectively. Treatment of **5** with $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at -78 °C to 10 °C or with camphorsulfonic acid (CSA) in $CH_2Cl_2$ produced **16** as the main product. It is supposed that C8 oxygen attack to the C5 carbon was easier than that of C1 oxygen under acidic conditions. On the other hand, treatment of **5** with NaH in THF at room temperature or with KOH in DMSO-$H_2O$ (3:1) at 140 °C recovered the starting epoxy alcohol **5**.

Next, we examined path B (Scheme 4). Enol silylether **18** was prepared from the ketone **6a** with TBSOTf and $Et_3N$. Treatment of **18** with dimethyldioxirane[9] in $CH_2Cl_2$-Acetone (1:1) without $H_2O$ at 0 °C produced epoxide **19**, which was spontaneously converted with a catalytic amount of CSA in $CH_2Cl_2$ at room temperature to α-hydroxyketone **20a** and α-silyloxyketone **20b** (as a 9:1 inseparable mixture of C6-epimer) in 7% and 82% yields, respectively. When the oxidation was carried out in the presence of $H_2O$, **20a** was the sole product. Several attempts[10] at the conversion of **20a** to **20b** were unsuccessful.



(a) i) LiHMDS, HMPA, THF, -78 °C, 2 h; ii) $PhNTf_2$, THF, -78 °C, 2 h, 65% (77% based on recovered **6a**); (b) $Me_2CuLi$, $Et_2O$, -78 °C, 30 min., 65~100%; (c) *m*CPBA, $NaHCO_3$, $CH_2Cl_2$, 0 °C, 2 h, 89%; (d) TBAF, THF, r.t., 1 h, ~100%; (e) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, r.t., 15 min. or -78 °C to 10 °C, 3 h; (f) CSA, $CH_2Cl_2$, -20 °C to r.t., 2 h.

**Scheme 3**



(a) TBSOTf, $Et_3N$, $CH_2Cl_2$, r.t., 2 h, ~100%; (b) dimethyldioxirane, acetone/$CH_2Cl_2$ (1:1), 0 °C, 15 min.; (c) CSA (cat.), $CH_2Cl_2$, r.t., 10 min., **20a**: 7% (from **18**), **20b** and C6-epimer of **20b**: 82% (from **18**); (d) MeLi, toluene, -78 °C, 5 min., **21**: 70% (from **20b**), **22** and C6-epimer of **22**: 19% (8:1, from **20b**); (e) AcOH/$H_2O$/THF (1:1:2), r.t., 6 h, 89% (from **21**); (f) PDC, $CH_2Cl_2$, r.t., 24 h, 80%; (g) TsCl, Pyridine, $CH_2Cl_2$, 0 °C, 15 h, 99%; (h) KH, THF, r.t., 1 h, 88%.

**Scheme 4**

Then, we investigated the formation of tertiary alcohol **21** from **20a** and **20b**. **20b** was reacted with MeLi in toluene at -78 °C to give **21** and **22** in 70% and 17% yields, respectively.[12] In $Et_2O$, **20b** afforded **21** and **22** in 34% and 39% yields, respectively.[12] Use of THF as a solvent resulted in **21** and **22** in 5% and 53% yields, respectively.[12] When **20b** was treated with MeMgBr, **22** was the major product, while **20a** was led to the undesired alcohol with MeLi or MeMgBr. Selective deprotection of the primary TBS group of **21** with AcOH-$H_2O$-THF (1:1:2) at room temperature gave diol **4**, which was oxidized with PDC in $CH_2Cl_2$ to afford the target lactone **2**.[13] Compound **4** was treated with TsCl and then with KH to obtain **3**.[14] Stereochemistries of **2** and **3** were determined by the differential NOE experiments of **3** and its diastereomers,[15] which were obtained from a mixture of **22** and its C6-epimer.

In conclusion, the substrate-controlled stereoselective synthesis of the GH ring part **2** or **3** of ciguatoxin was accomplished in a racemic form. We believe that the synthetic path leading to **2** or **3** would be suitable for construction of the corresponding optically active derivatives by use of an established chiral reducing agent[16] to **7**. Further studies toward the total synthesis of **1** are now in progress in our laboratory.

**References and Notes**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3. For other synthetic works, see: E. Alvarez, M. T. Díaz, R. Pérez, J. L. Ravero, A. Reguerio, J. A. Vera, D. Zurita, and J. D. Martín, *J. Org. Chem.*, **59**, 2848 (1994); M. Sasaki, M. Inoue, and K. Tachibana, *J. Org. Chem.*, **59**, 715 (1994); H. Oguri, S. Hishiyama, T. Oishi, and M. Hirama, *Synlett.*, 1252 (1995); S. Hosokawa and M. Isobe, *Synlett*, 351 (1996); T. Oka, K. Fujiwara, and A. Murai, *Tetrahedron*, **52**, 12091 (1996); and other references cited there.
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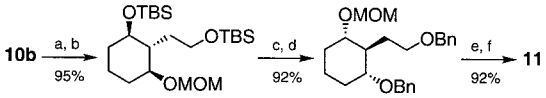
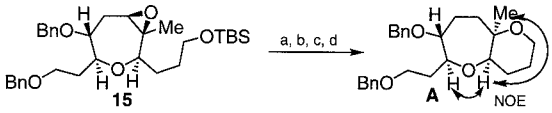
6. The ketone **11** was prepared from **10b** as follows:



(a) TBSCl, $Et_3N$, DMAP, $CH_2Cl_2$, r.t., 1.5 day; (b) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, r.t., 3 days; (c) TBAF, THF, r.t., 18 h; (d) BnBr, *t*-BuOK, TBAI, THF, 0 °C, 1.5 h; (e) 6M HCl in $H_2O$-MeOH (1:5), r.t., 40 h; (f) Swern oxid., -50 °C, 2 h.

7. K. Tsushima, K. Araki, and A. Murai, *Chem. Lett.*, 1313 (1989); F. Feng and A. Murai, *Chem. Lett.*, 1587 (1992).
8. This stereochemistry was determined by differential NOE experiment on bicyclo compound **A**, which was derived from **15** as follows:

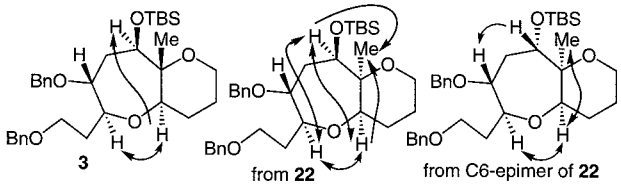


(a) $LiEt_3BH$, THF, r.t., 20 h; (b) KF, 18-Crown-6, $CH_3CN$, reflux, 1 day; (c) TsCl, Pyridine, $CH_2Cl_2$, r.t., 1 day; (d) KH, THF, r.t., 1 day.

9. R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989); W. Adam, L. Hadjiarapoglou and X. Wang, *Tetrahedron Lett.*, **30**, 6947 (1989).
10. Attempted conditions: TBSCl, imidazole; TBSOTf, 2,6-lutidine; $TBSOCH_2CH{=}CH_2$, PTS or $I_2$.[11]
11. T. Morita, Y. Okamoto, and H. Sakurai, *Tetrahedron Lett.*, **21**, 835 (1980); A. Hosomi and H. Sakurai, *Chem. Lett.*, 85 (1981).
12. **22** and the C6-epimer of **22** were an inseparable mixture. The yield of **22** was calculated from the integral ratio of its $^1$H-NMR spectrum. The C6-epimer of **21** was not given from the C6-epimer of **20b** under several conditions.
13. **2**: $^1$H-NMR (270 MHz, $CDCl_3$), δ(ppm) 7.26-7.37 (10H, m), 4.57 (1H, d, J=12 Hz), 4.51 (1H, d, J=12 Hz), 4.43 (1H, d, J=12 Hz), 4.42 (1H, d, J=12 Hz), 4.15 (1H, dd, J=3, 11 Hz), 3.91 (1H, dt, J=1, 7 Hz), 3.70 (1H, dd, J=6, 11 Hz), 3.44-3.60 (3H, m), 2.63 (1H, ddd, J=2, 10, 19 Hz), 2.51 (1H, ddd, J=9, 11, 19 Hz), 2.00 (1H, ddd, J=3, 6, 15 Hz), 1.63-1.98 (6H, m), 1.34 (3H, s), 0.92 (9H, s), 0.18 (3H, s), and 0.13 (3H, s).
14. **3**: $^1$H-NMR (400 MHz, $C_6D_6$), δ(ppm) 7.34 (2H, d, J=8 Hz), 7.30 (2H, d, J=7 Hz), 7.15-7.20 (5H, m), 7.06-7.11 (1H, m), 4.47 (1H, d, J=12 Hz), 4.35 (1H, d, J=12 Hz), 4.31 (1H, d, J=12Hz), 4.29 (1H, dd, J=3, 11 Hz), 4.28 (1H, d, J=12 Hz), 4.09 (1H, br dd, J=5, 9 Hz),

3.55 (1H, dd, J=5, 11 Hz), 3.50 (1H, ddd, J=6, 8, 9 Hz), 3.37-3.44 (3H, m), 3.26 (1H, dt, J=2, 12Hz), 2.01 (1H, ddd, J=3, 6, 15 Hz), 1.90 (1H, ddd, J=2, 11, 15 Hz), 1.54-1.72 (3H, m), 1.48 (1H, br ddt, J=4, 12, 12 Hz), 1.34 (3H, s), 1.25-1.39 (1H, m), 1.13 (9H, s), 1.10-1.18 (1H, m), 0.32 (3H, s), and 0.29 (3H, s).

15. The results of differential NOE experiments.

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