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The Construction of the A,B,C-ring System of Ciguatoxin

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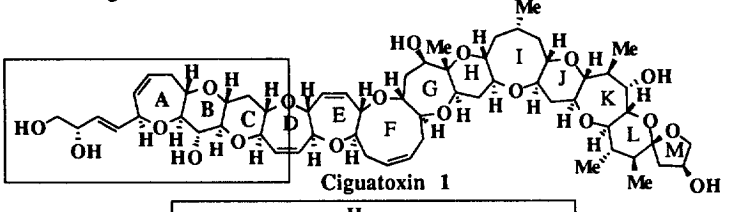
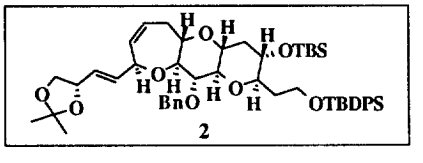
Abstract: The first construction of the A,B,C-ring system having all of the natural substituents in ciguatoxin was achieved from D-glucose. © 1997 Elsevier Science Ltd.

Ciguatoxin **1** was isolated as the principal toxin causing ciguatera from moray eel *Gamnothorax javanicus*. The structure of **1** determined by Yasumoto *et al.* has a characteristic polycyclic system including 13 medium-sized cyclic ethers.[1] Its interesting biological activities and limited availability from natural sources have made **1** one of the most challenging synthetic target molecules. The syntheses of the model compounds corresponding to the A,B,C-ring system of **1** have been recently accomplished by the Isobe and Hirama groups.[2] We now describe herein the first substrate-controlled and stereoselective synthesis of the natural enantiomer of the A,B,C-ring system **2** including the completely constructed C-ring part from commercially available D-glucose.

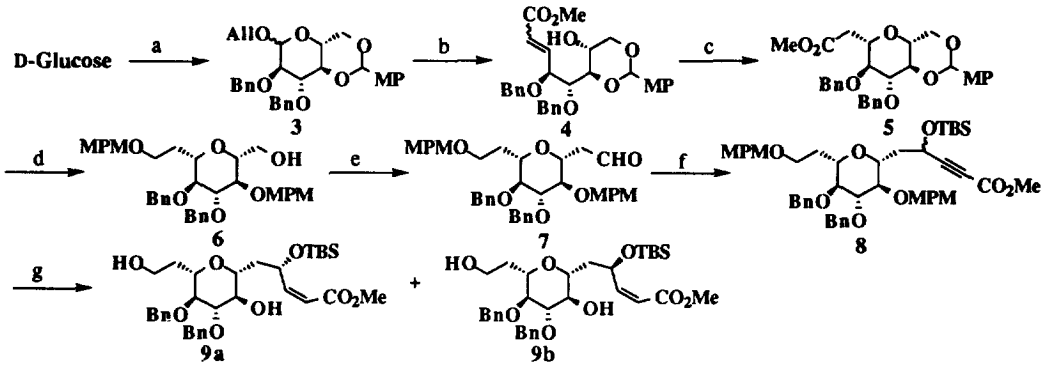


Ciguatoxin **1**



2

The synthesis was started with conversion of D-glucose *via* the allyl glycoside,[3] 4-methoxybenzylidene acetal, and bis-benzyl ether to afford **3** (Scheme 1). The allyl group of **3** was detached,[4] followed by Wittig reaction with $Ph_3P{=}CHCO_2Me$ and hetero-conjugate cyclization with NaH, to give **5** in the respective high yields. The ester group of **5** was reduced with $LiAlH_4$ and the resulting hydroxy group was protected with MPMCl. Then, the 4-methoxybenzylidene acetal was selectively cleaved with DIBAL to afford **6**. After tosylation of the hydroxy group of **6**, the tosylate was substituted to the CN group with KCN which was reduced with DIBAL to the corresponding aldehyde **7**. Coupling reaction of **7** with lithiated methyl propiolate proceeded smoothly to obtain an $\alpha{:}\beta{=}2{:}5$ mixture of acetylene alcohols, and the respective hydroxy groups were protected with TBSOTf to yield **8**. Hydrogenation of **8** with Lindlar catalyst and the subsequent MPM deprotection with DDQ led to separation of **9a** and **9b**.



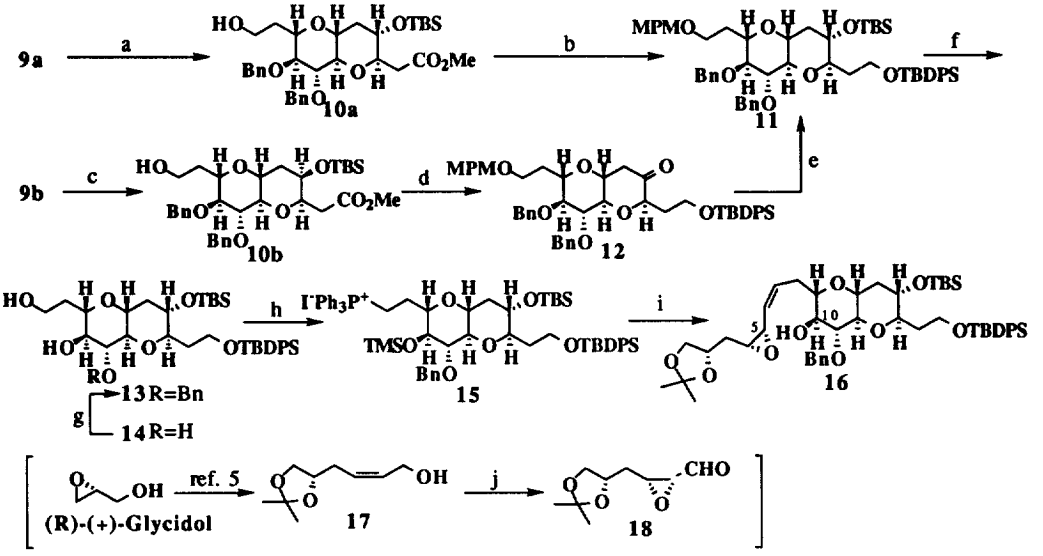
Reagents and Conditions: a) allyl alcohol, TfOH, 80 °C, 2 d; 4-MeO-PhCH(OMe)$_2$, PTS·H$_2$O, DMF, aspirator pressure, 50 °C, 4 h (67% for 2 steps); BnBr, NaH, THF-DMF (1:1), r.t., 5 h (62%); b) (Ph$_3$P)$_3$RhCl, *i*-Pr$_2$NEt, EtOH, reflux, 4 h; HgCl$_2$, HgO, acetone-H$_2$O (9:1), r.t., 1 h (92% for 2 steps); Ph$_3$P=CHCO$_2$Me, PhH, reflux, 24 h (99%, *E*:*Z*=4:1); c) NaH, THF, r.t., 16 h (94%); d) LiAlH$_4$, ether-THF (4:1), 0 °C, 30 min (98%); MPMCl, KH, TBAI, THF, r.t., 3 h (quant.); DIBAL, CH$_2$Cl$_2$, 0 °C, 1 h (95%); e) TsCl, NEt$_3$, DMAP, CH$_2$Cl$_2$, r.t., 6 h (quant.); KCN, DMSO, 50 °C, 7 h (99%); DIBAL, CH$_2$Cl$_2$, -78 °C, 30 min (95%); f) methyl propiolate, LDA, THF, -78 °C, 1 h (98%, α:β=2:5); TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, r.t., 15 min (97%); g) H$_2$, Lindlar cat., MeOH-PhH (6:1), r.t., 7 d (99%); DDQ, CH$_2$Cl$_2$-H$_2$O (10:1), r.t., 30 min (**9a**, 22%; **9b**, 58%).

Scheme 1.

The hetero-conjugated cyclization of **9a** with NaH in THF gave rise to a mixture of the desired product and its dimers. Furthermore, the crude products were treated with *t*-BuOK in MeOH[5] to afford **10a** in 91% total yield from **9a** (Scheme 2). Protection of the hydroxy group of **10a** with *p*-methoxybenzyl-2,2,2-trichloroacetimidate and TfOH,[6] followed by reduction and silylation, provided **11** corresponding to the B,C-ring part of **1**. On the other hand, conversion of **9b** involved the hetero-conjugated cyclization with NaH in THF and with *t*-BuOK in MeOH to get **10b** in 99% combined yield. The hydroxy group of **10b** was protected as the MPM group and the ester group was reduced with LiAlH$_4$ to yield the corresponding primary alcohol. After removal of the TBS group with TBAF, the primary hydroxy group was selectively protected with TBDPSCl, and the secondary was oxidized to the ketone under the Swern conditions to yield **12**. The highly selective reduction of **12** with LiAlH$_4$ obtained the corresponding α-OH which was protected with TBSOTf to lead **11**. The MPM ether of **11** was detached with DDQ, and the Bn ether of the product was hydrogenated with Pd(OH)$_2$/C to get a 1:1 mixture of diol **13** and triol **14**. The compound **14** was converted into **13** *via* acetonide formation of the 1,4-diol, Bn-ether protection of the rest hydroxy group, and hydrolysis of the acetonide group. The selective mono-tosylation of the diol **13** followed by displacement of the primary tosyl group with NaI was led to the iodide. Protection of the secondary alcohol in the iodide as the TMS ether and further reaction with PPh$_3$ obtained the phosphonium salt **15** in an excellent total yield.

Construction of the aldehyde **18** commenced with the known allyl alcohol **17** which was prepared in 6 steps from commercially available (*R*)-(+)-glycidol.[5] The compound **17** was oxidized under the Sharpless conditions[7] to afford the epoxy alcohol (>95% de) which was oxidized to the aldehyde **18** under the Swern conditions.

Generation of the ylide from **15** with NaHMDS followed by addition of aldehyde **18** produced the *Z*-olefin as a sole product which was desilylated to the alcohol **16** in moderate yield. The results might be due to poor nucleophilicity of the ylide as well as enolization of the aldehyde under the basic conditions. Many efforts to solve these problems were fruitless.



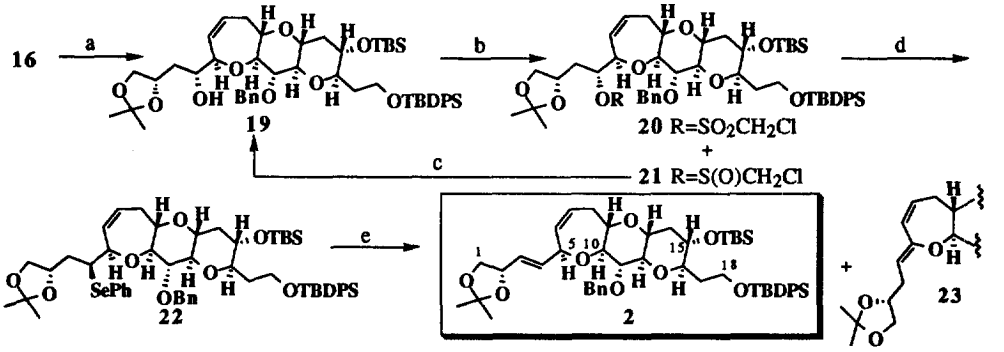
Reagents and Conditions: a) NaH, THF, -40 °C→r.t., 2 h; *t*-BuOK, MeOH, r.t., 18 h (91% for 2 steps); b) $MPMOC(=NH)CCl_3$, TfOH, ether, r.t., 10 min (75%); $LiAlH_4$, ether, -10 °C, 30 min (quant.); TBDPSCl, NEt_3, DMAP, CH_2Cl_2, r.t., 9 h (95%); c) NaH, THF, -40 °C→r.t., 4.5 h; *t*-BuOK, MeOH, r.t., 14 h (99% for 2 steps); d) $MPMOC(=NH)CCl_3$, TfOH, ether, r.t., 10 min (86%); $LiAlH_4$, ether, -10 °C, 30 min (99%); TBAF, THF, r.t., 1 h (quant.); TBDPSCl, NEt_3, DMAP, CH_2Cl_2, r.t., 12 h (quant.); Swern oxid. (quant.); e) $LiAlH_4$, ether, -20 °C, 15 min (99%); TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 1 h (97%); f) DDQ, CH_2Cl_2-H_2O (10:1), r.t., 40 min (quant.); H_2, $Pd(OH)_2/C$, EtOH-EtOAc (5:1), r.t., 7 d (**13**, 44%; **14**, 44%; recovery 5%); g) PTS·H_2O, acetone, r.t., 30 min (4 cycles, total 95%); BnBr, NaH, TBAI, THF, r.t., 31 h (99%); PTS·H_2O, MeOH, r.t., 30 min (94%); h) TsCl, NEt_3, DMAP, CH_2Cl_2, r.t., 20 h (90%); NaI, acetone, 50 °C, 8 h (86%); TMSOTf, NEt_3, CH_2Cl_2, -10 °C, 10 min (98%); PPh_3, MeCN, 60 °C, 27 h (98%); i) NaHMDS (1.5 eq), THF, r.t., 30 min, then **18** (2.0 eq), r.t., 30 min (38%, based on **15**); K_2CO_3, MeOH, 0 °C, 1.5 h (96%); j) (+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, MS4A, CH_2Cl_2, -20 °C, 18 h (74%, >95% de); Swern oxid. (93%).

Scheme 2.

Construction of **19** by A-ring closure reaction was succeeded only under the conditions using $Eu(fod)_3$ in toluene (Scheme 3),[8] although the other conditions led to failure [for example, some basic treatment or use of an acid such as CSA, $Zn(OTf)_2$, $La(OTf)_2$, $VO(acac)_2$, or $Eu(dpm)_3$]. These results reveal that there might be some dependence of acidity strengths of the respective Lewis acids as well as that of the bond lengths of chelation with O-functions of the epoxy alcohol. Eventually, the C-10 hydroxy group in **16** could exist near the C-5 epoxide carbon only in the case of $Eu(fod)_3$.

Finally, transformation of the compound **19** into the A,B,C-ring system **2** was achieved as follows (Scheme 3). The secondary alcohol of **19** was converted on treatment with $ClCH_2SO_2Cl$[9] into chloromethanesulfonate **20** as well as sulfinate **21**, which, however, could be returned to **19** with DBU. Phenylselenation of **20** proceeded smoothly *via* SN2 reaction to afford the selenide **22**, of which the *syn* elimination with H_2O_2 gave rise to the desired **2** along with the conjugated diene **23** in good yields.[10,11] The product by *anti* elimination with DBU of **20** was only **23** in 70% yield.

Our synthetic route is characterized by the following three points; i) use of the readily available D-glucose as the starting material; ii) construction of the substituted A-ring by the novel ring-closure reaction of the vinylic epoxy alcohol; iii) introduction of the necessary substituents in the C-ring aiming to the linear construction of the D-ring.



Reagents and Conditions: a) $Eu(fod)_3$ (3.0 eq), toluene, 80 °C, 15 h (38%); b) $ClCH_2SO_2Cl$, pyridine, DMAP, CH_2Cl_2, r.t., 2 h (**20**, 60%; **21**, 34%); c) DBU, toluene, reflux, 1 h (88%); d) $Na^+[PhSeB(OEt)_3]^-$, EtOH, reflux, 3 h (62%); e) H_2O_2, pyridine, CH_2Cl_2, 0 °C→r.t., 1 h (**2**, 59%; **23**, 39%).

Scheme 3.

References and Notes

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11. **2**: $[\alpha]_D^{26}$ +30.2° (*c* 0.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 7.65 (4H, br d, *J* = 7 Hz), 7.40-7.19 (11H, m), 5.89 (1H, br dd, *J* = 5, 16 Hz, H-4), 5.78 (1H, br ddd, *J* = 1, 7, 16 Hz, H-3), 5.79-5.75 (2H, m, H-6 and 7), 4.71(1H, d, *J* = 11 Hz), 4.64 (1H, d, *J* = 11 Hz), 4.59-4.56 (1H, br m, H-5), 4.52 (1H, br q, *J* = 7 Hz, H-2), 4.06 (1H, dd, *J* = 6, 8 Hz, H-1), 3.89 (2H, br t, *J* = 7 Hz, H-18), 3.53 (1H, t, *J* = 8 Hz, H-1), 3.46-3.38 (2H, m, H-11 and 10), 3.37 (1H, br dt, *J* = 5, 9 Hz, H-15), 3.32-3.25 (2H, m, H-16 and 9), 3.12-3.07 (2H, m, H-12 and 13), 2.64 (1H, br ddd, *J* = 4, 8, 16 Hz, H-8), 2.39-2.29 (1H, m, H-8), 2.32-2.25 (1H, m, H-14-eq), 2.25-2.16 (1H, m, H-17), 1.67-1.50 (2H, m, H-17 and 14-ax), 1.42 (3H, s), 1.40 (3H, s), 1.04 (9H, s), 0.90 (9H, s), and 0.08 (6H, s); IR (film), ν_{max} 2924, 2852, 1714, 1466, 1380, 1088, 856, 828, and 776 cm^{-1}; HR-FD/FI-MS calcd. for $C_{50}H_{70}O_8Si_2$ (M^+) 854.4611, found *m/z* 854.4634.

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