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Stereoselective Synthesis of a KLM Ring Model of Ciguatoxin: Confirmation of the C54 Stereochemistry

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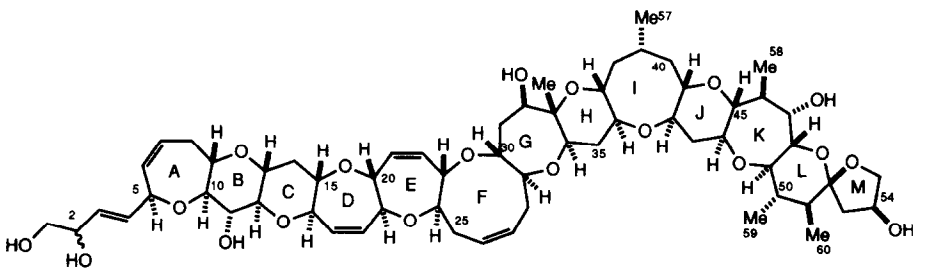
Abstract: A ciguatoxin KLM ring model and its C54 epimer were stereoselectively synthesized. Comparison of their ^{1}H NMR data with that on the natural toxin established the earlier stereochemical assignment at the C54 position.

Ciguatoxin (**1**) and its congeners are the toxic principles of ciguatera, which is known as the most widespread among food poisonings of dinoflagellate origin.[1] The toxin molecule **1**, consisting of 12 fused rings of cyclic ethers ranging from six- to nine-membered, where another five-membered is spirally attached, is one of the most potent neurotoxins and binds to the same site of the voltage-dependent sodium channels as structurally similar brevetoxins.[2] The whole structure of **1** was elucidated including relative stereochemistry except at the C2 position using a purified sample of only 0.35 mg. 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 highly specific immunoassay for its detection. In addition, stereochemistry at its C54 position, which was suggested on the basis of NOE experiments,[1a] still remained somewhat ambiguous. In the course of synthetic studies toward the ciguatoxins and their structural fragments including the KLM ring portion,[3] establishment of the C54 stereochemistry was required. In this letter, we report a stereoselective synthesis of a KLM ring model **11a** and its C54 epimer **11b**, and consequent confirmation of the relative stereochemistry at the C54 position of ciguatoxin.

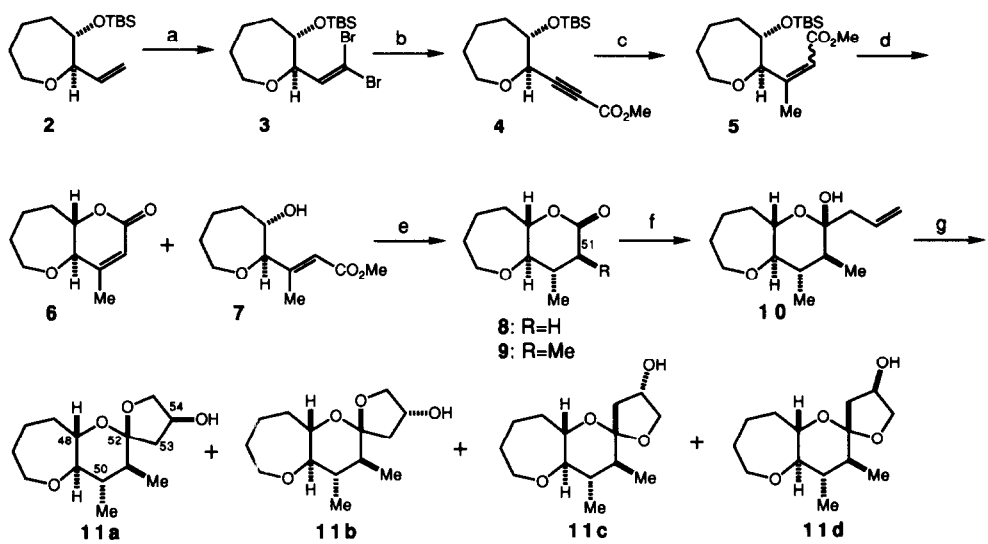


1: Ciguatoxin

A known compound **2**[4] was selected as a starting material in the present syntheses (Scheme 1). Ozonolysis of **2** followed by dibromoolefination afforded **3**. Exposure of the dibromoolefin **3** to Corey-Fuchs

conditions[5] and quenching the intermediate acetylenic anion with methyl chloroformate gave the alkynyl ester **4**. Treatment of **4** with MeMgBr in the presence of CuI yielded a *E*/*Z* mixture of α,β-unsaturated esters **5** in quantitative yield, favoring the desired *Z*-isomer. Removal of the silyl protecting group from the mixture and lactonization with camphorsulfonic acid afforded the desired unsaturated lactone **6** accompanied by **7**. Catalytic hydrogenation of the lactone **6** occurred only from the β-face to yield **8** as a sole stereoisomer in quantitative yield and subsequent methylation of the lactone enolate derived from **8** afforded **9** with the desired configuration at C51 in 77% yield with 9% recovered starting material. Introduction of the allyl group as a three-carbon unit for the construction of the spirally attached M ring gave hemiketal **10**. Osmylation of **10** was accompanied by the spiroketal formation to give a mixture of four isomers **11a-d**, which were easily separated by silica gel column chromatography. In their ^{1}H NMR spectra, 48-H and 50-H[6] were distinctly shifted downfield in **11a** and **11b** from those in **11c** and **11d**.[7] Relatively large NOEs were also observed between 48-H and 53α-H in **11c** and **11d**. Treatment of **11c** and **11d** with trifluoroacetic acid in CH_2Cl_2 afforded **11a** and **11b**, respectively. These evidences allowed us to conclude that **11a** and **11b** were the thermodynamically more stable isomers at the C52 position with equatorially oriented C53[8] and that **11a** and **11c** were the respective diastereoisomers of **11b** and **11d** at the C54 position .

Scheme 1[a]



[a]Reagents and conditions: (a) (i) O_3, CH_2Cl_2, -78 °C; Me_2S, Ph_3P, -78 °C to RT; (ii) CBr_4, Ph_3P, CH_2Cl_2, 0 °C (2 steps 91%); (b) *n*-BuLi, $ClCO_2Me$, THF, -78 °C (94%); (c) MeMgBr, CuI, THF, -78 °C (98%); (d) (i) CSA, MeOH, RT; (ii) CSA, PhH, reflux (**6**: 62%; **7**: 38%); (e) (i) H_2, 5% Pd-C, EtOAc, RT (93%); (ii) LDA, MeI, THF, -78 °C (77%); (f) AllylMgBr, THF, -78 °C (quant.); (g) OsO_4, CH_3CN-H_2O, RT; Na_2SO_3 (**11a**: 35%, **11b**: 23%, **11c**: 9%, **11d**: 24%).

In addition to indication by the results of differential NOE experiments[9] as shown in Figure 1, the relative stereochemistry at the C54 position of **11a** and **11b** was assigned by determining the absolute configuration at this position by the following two independent experiments. Firstly, the improved Mosher's method developed by Ohtani *et al.*[10] was applied on **11a**, *e.g.*, both the (*S*)- and (*R*)-MTPA esters of **11a** were synthesized [(2-

methoxy-2-(trifluoromethyl)phenylacetic acid, DCC, DMAP, CH_2Cl_2] and the values of $\Delta\delta = \delta(S) - \delta(R)$ were obtained as shown in Figure 2. Since all assigned protons with positive and negative $\Delta\delta$ values are found on the right and left sides of the MTPA plane, respectively, they indicated the assigned stereochemistry at the C54 position of **11a**. Secondly, Corey's asymmetric osmylation [OsO_4, *N, N'*-bis(2,4,6-trimethylbenzyl)-(*S,S*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, -90 °C; saturated aq.$NaHSO_3$-THF (1:1), reflux][11] of **10** followed by acid treatment gave **11a** as the major product in 82% yield and 65% diastereoselectivity, while the conventional osmylation gave little selectivity as described above.

Figure 1

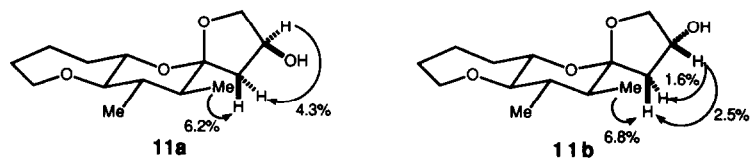
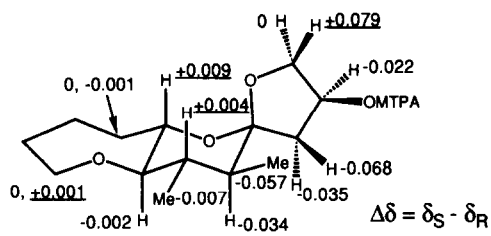


Figure 2



Examination of the chemical shifts and vicinal spin-spin coupling constants in the ^1H NMR spectra of thus assigned **11a** and **11b** demonstrated that the ^1H NMR data observed for **11a**, and not for **11b**, matched well with the reported values[1a] for ciguatoxin (Table 1). In conclusion, stereochemistry of the hydroxy group at the C54 position of ciguatoxin was confirmed to be β configuration represented by structure **1**. Further synthetic studies toward ciguatoxins and their elongated structural fragments are currently in progress.

Table 1. Selected ^1H and ^{13}C-NMR data of **11a**, **11b**, and ciguatoxin.[a]

position	**11a**[b]		**11b**[b]		ciguatoxin[c]	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
50	1.83 (m)	39.30	1.78 (m)	38.82	2.01 (-)	38.98
51	1.54 (m)	41.82	1.45 (m)	42.41	1.67 (-)	42.15
52		108.80		108.31		109.64
53α	2.39 (dd, 13.5, 7.0)	45.34	2.42 (dd, 13.4, 8.1)	44.52	2.40 (dd, 13, 8)	45.75
53β	2.29 (dd, 13.5, 3.4)		2.18 (dd, 13.4, 4.6)		2.35 (dd, 13, 5)	
54	4.83 (m)	70.45	4.58 (m)	70.44	4.86 (m)	70.69
55	4.11 (dd, 9.0, 1.9)	74.74	4.05 (dd, 8.5, 6.1)	74.11	4.18 (dd, 10, 2)	75.10
55	4.16 (dd, 9.0, 4.8)		4.17 (dd, 8.5, 6.3)		4.19 (dd, 10, 5)	
59	1.06 (d, 6)	15.21	1.03 (d, 6)	15.13	1.32 (d, 6)	16.18
60	1.16 (d, 7)	13.56	0.89 (d, 7)	13.40	1.24 (d, 7)	13.92

a) The ^1H NMR spectra were measured in pyridine-d_5 and the ^{13}C-NMR spectra were measured in pyridine-d_5/D_2O (20:1).

b) The spectra were recorded on a Bruker AM-500 spectrometer. c) The spectra were recorded on a JEOL GSX-400 spectrometer.[1a,b)]

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References and Notes

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6. The numbering adopted in this paper corresponds to that of ciguatoxin.
7. Chemical shifts of protons at the C48 and C50 position of **11a-d** (C_6D_6, 500 MHz):

position	**11a**	**11b**	**11c**	**11d**
48-H	3.82	3.82	3.36	3.18
50-H	1.91	1.81	1.22	1.23

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