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# Enantioselective Synthesis of the AB Ring Fragment of Gambiertoxin 4B. Implication for the Absolute Configuration of Gambiertoxin 4B and Ciguatoxin

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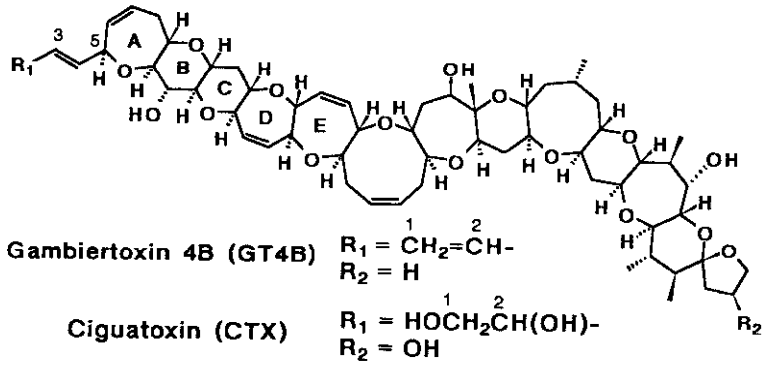
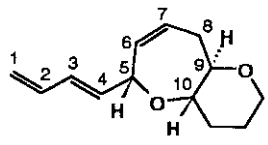
*Key Word:* Ciguatoxin; Gambiertoxin; Absolute configuration; CD; Enantioselective synthesis

***Abstract:*** The AB ring framework of gambiertoxin 4B which has a butadienyl substituent on the tetrahydrooxepin ring A has been synthesized stereoselectively and its CD spectrum suggests that gambiertoxin 4B and ciguatoxin have *5R* configuration.

Twenty thousand of people in subtropical and tropical regions have suffered annually from ciguatera caused by poisonous fishes dwelling in coral reefs. In 1989 Yasumoto et al. established the whole structures including relative stereochemistry of the causative principle, ciguatoxin (CTX), isolated from moray eel, *Gymnothorax javanicus*, and its congener, gambiertoxin 4B (GT4B), from epiphytic dinoflagellate, *Gambierdiscus toxicus*.[1,2] Extremely low accessibility of these toxins, however, hampers further studies on their absolute configuration, pharmacological studies at the molecular level[1] and development of immunoassay for differentiating poisonous fishes. Therefore, determination of the absolute stereochemistry and their chemical syntheses are critical and of great interest. In this letter we report a stereoselective synthesis of AB ring system of GT4B and an indication of the absolute configuration.

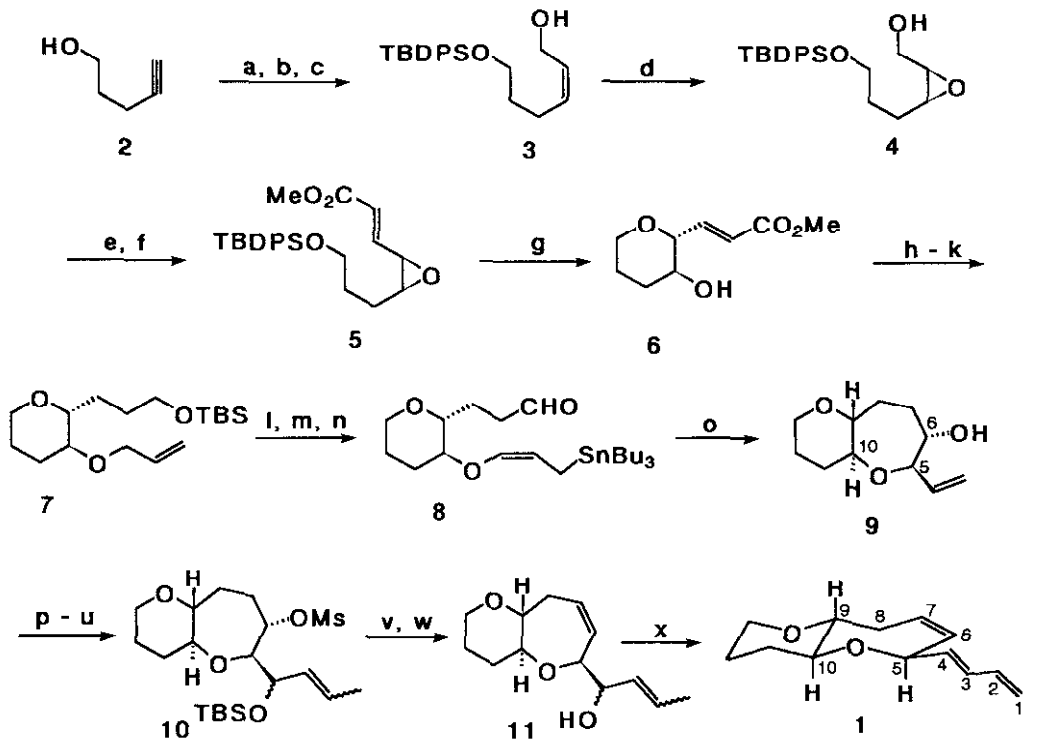


**1**
(5*S*, 9*R*, 10*S*)

GT4B exhibits a characteristic UV absorption maximum at 222 nm (ε 27000) in acetonitrile due to the butadienyl substituent as shown in Figure 1. Although a distinct Cotton effect at the corresponding wave length has not been observed on the CD spectra [Figure 1: $\lambda_{ext}$ 207 nm (Δε -7.4); 239 nm (Δε +0.69) in $CH_3CN$], Cotton effect at the longer wave length (239 nm) must be derived from the interactions of the conjugated diene with the allyl ether system of the ring A, which is consistent with the absence of the corresponding band in CTX (Figure 1). Since molecular model indicates that the ABCDE ring system of GT4B is rigid and flat, the conformation of the butadienyl allyl ether system critical for such Cotton effects would not be affected by the condensation of the CDE rings. Therefore, AB ring model 1 was expected to show similar Cotton effect curve to that of GT4B. Synthesis of enantiomerically defined 1 and its CD spectra would provide an evidence for the absolute stereochemistry. The (5*S*, 9*R*, 10*S*)-enantiomer 1 was synthesized as shown in Scheme 1.

## Scheme 1




a) TBDPSCl, imidazole, DMF, 100%; b) BuLi, $(HCHO)_n$, THF, -90°C - rt, 97%; c) $H_2$, Lindlar cat., MeOH, 99%; d) $Ti(OiPr)_4$, D-(-)-DET, TBHP, $CH_2Cl_2$, -20°C, 88%, 89%ee; e) $SO_3$-Py, DMSO, $NEt_3$, 100%; f) $Ph_3P{=}CHCO_2Me$, benzene, 87%; g) $Bu_4NF$, THF, then $Pd(PPh_3)_4$, $PPh_3$, $CHCl_3$, 74%; h) $H_2$, 5%-Pd/C, MeOH, 99%; i) $LiAlH_4$, $Et_2O$, 0°C, 100%; j) TBSCl, imidazole, DMF, 0°C, 94%; k) KH, allyl bromide, THF, 0°C - rt, 97%; l) $Bu_4NF$; m) sec-BuLi, $Bu_3SnCl$, THF, -78°C, 85% from 7; n) MeMgBr, t-BuOH, THF, 0°C - rt, then 1,1'-(diazocarbonyl)-dipiperidine, THF, 0°C, 90%; o) $BF_3$-$Et_2O$, $CH_2Cl_2$, -78°C; p) Ethyl vinyl ether, PPTS, $CH_2Cl_2$, 97% from 8; q) $O_3$, $CH_2Cl_2$, -78°C, then $PPh_3$; r) 1-Bromo-1-propene, Mg, $Et_2O$, -78°C - rt, 87% (2 steps); s) TBSCl, imidazole, DMF, 91%; t) PPTS, EtOH, 77%; u) MsCl, $NEt_3$, $CH_2Cl_2$, 0°C, 87%; v) DBU, toluene, 111°C, 82%; w) $Bu_4NF$, THF, 0°C, 100%; x) 2,4-dinitrobenzenesulfenyl chloride, $NEt_3$, $ClCH_2CH_2Cl$, 83°C, 72%.

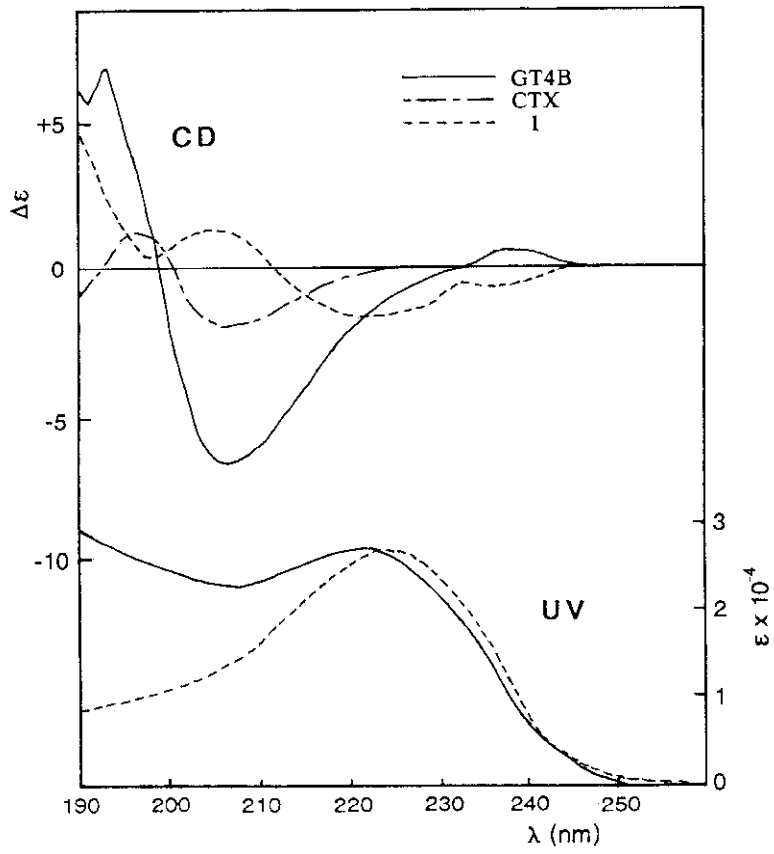
4-Pentyn-1-ol (2) was converted to (2*R*, 3*S*)-epoxy alcohol **4** (89% ee)[3] through Katsuki-Sharpless asymmetric epoxidation of 3.[4] Oxidation of **4** and subsequent Horner-Wittig reaction gave γ,δ-epoxy-α,β-unsaturated ester **5**, which was regio- and stereoselectively cyclized to 2,3-trans-disubstituted tetrahydropyran **6** by using palladium catalyst.[5] This unsaturated ester was reduced to a saturated alcohol and protected selectively as t-butyldimethylsilyl (TBS) ether, and the remaining secondary alcohol was allylated to afford **7**. Treatment of **7** with sec-BuLi and tributyltin chloride followed by oxidation[6] gave the aldehyde **8**. $BF_3$ etherate promoted cyclization[7] of **8** provided the AB ring skeleton **9** stereoselectively. NOE experiments for TBS ether of **9** supported the stereochemistry at C5, C6, and C10. Regio- and stereoselective construction of 1, 3(E), 6-triene system was achieved as follows.[8] The vinyl group of **9** was transformed to aldehyde, and Grignard addition reaction accompanied by protection and deprotection procedures of alcohols afforded a stereoisomeric mixture **10**. Regioselective elimination[8] of the mesylate group of **10** was performed by refluxing it in toluene in the presence of DBU to give **11** after deprotection of TBS ether. Sequential sulfenylation-[2,3]sigmatropic rearrengement-sulfoxide elimination reactions[9] of **11** by using 2,4-dinitrobenzenesulfenyl chloride and triethylamine proceeded smoothly to afford trans-butadiene **1** as a sole product without migration of the 6,7-double bond.[8]

$^1$H NMR chemical shifts and coupling constants of **1** are in good agreement with those of GT4B (Table 1). This demonstrates that the conformations of the ring skeleton and the trans-butadienyl substituent of **1** are identical with those of the GT4B as expected. CD Spectrum of **1** (Figure 1) shows a negative Cotton effect at the longest wave length (237 nm, Δε -0.83), which suggests that GT4B (239 nm, Δε +0.69) as well as CTX[1] has a configuration (5*R*, 9*S*, 10*R*) opposite to **1**. In addition, another Cotton effect relevant to the UV band of the conjugated diene [$\lambda_{max}$ 224 nm (ε 27000)] appeared at 223 nm (Δε -1.8). The reason why the corresponding band is not apparent in GT4B might be owing to the overlap of the strong negative Cotton effect at 207 nm (Δε -7.4) to the putative weak positive Cotton effect at that region. The origin of the intenseness of the Cotton effect at 207 nm in GT4B is not clear at this moment. Further synthetic studies as well as decisive CD analyses are currently underway and will be reported in due course.

**Table 1.** $^1$H NMR Chemical Shifts and Coupling Constants of **1** and GT4B in $CD_3CN$

| Position | 1 (600 MHz) | GT4B (400 MHz) |
|---|---|---|
| H-1 | δ 5.05 (ddd, J=10.5, 1.5, 0.9 Hz) | δ 5.07 (dd, J=9.8, 2.1 Hz) |
| H-1 | 5.19 (ddd, J=17.0, 1.5, 0.9 Hz) | 5.23 (dd, J=16.7, 2.1 Hz) |
| H-2 | 6.34 (dt, J=17.0, 10.5 Hz) | 6.34 (ddd, J=16.7, 10.6, 9.8 Hz) |
| H-3 | 6.24 (dddt, J=15.0, 10.5, 1.6, 0.9 Hz) | 6.30 (ddd, J=15.0, 10.6, 1.5 Hz) |
| H-4 | 5.74 (dd, J=15.0, 5.8 Hz) | 5.77 (dd, J=15.0, 5.9 Hz) |
| H-5 | 4.57 (br) | 4.55 (br d, J=5.9 Hz) |
| H-6 | 5.75 (ddd, J=11.0, 4.1, 2.8 Hz) | 5.76 |
| H-7 | 5.82 (dddd, J=11.0, 8.0, 4.1, 2.5 Hz) | 5.76 |
| H-8 | 2.30-2.37 (m) | 2.32 (m) |
| H-8 | 2.38 (ddd, J=15.0, 8.0, 4.0 Hz) | 2.49 (ddd, J=15.5, 6.7, 4.1 Hz) |
| H-9 | 2.93 (ddd, J=9.9, 8.6, 4.0 Hz) | 3.15 (ddd, J=10.4, 8.8, 4.1 Hz) |
| H-10 | 3.31 (ddd, J=10.8, 8.6, 4.6 Hz) | 3.25 (t, J=8.8 Hz) |

**Figure 1.** UV and CD Spectra of GT4B, CTX, and 1 in $CH_3CN$





**References and Notes**

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2. The relative stereochemistry at C2 of CTX is not known.
3. Determined by NMR analysis with a chiral shift reagent, (+)-Eu-DPPM.
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7. For the related intramolecular cyclization of allyltin acetals promoted by $TiCl(OiPr)_3$, see: Yamada, J.; Asano, T.; Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 6066-6068.
8. The 1,3-butadiene substituent has to be introduced after the 6,7-double bond is made. Otherwise, migration of the 6,7-double bond leading to the conjugated 1,3,5-triene occurs quickly under the basic elimination conditions of the mesylate.
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