# Total Synthesis of Antillatoxin, an Ichthyotoxic Cyclic Lipopeptide, Having the Proposed Structure. What Is the Real Structure of Antillatoxin?

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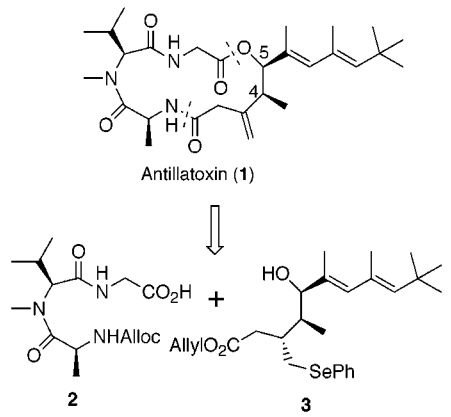
Antillatoxin (**1**) is an ichthyotoxic metabolite from the marine cyanobacterium *Lyngbya majuscula* collected in Curaçao.[1] Goldfish toxicity measurements with antillatoxin shows it to be among the most ichthyotoxic metabolites isolated to date from a marine plant ($LD_{50}$ = 0.05 $\mu$g/mL). Antillatoxin is a structurally novel lipopeptide with a high degree of methylation. Especially, it has a conjugated diene that contains a *tert*-butyl group and the isolated terminal olefin. Therefore, antillatoxin is a structurally and biologically attractive marine natural product. We now wish to report the total synthesis of antillatoxin having the reported structure **1**.[2] In our convergent strategy, antillatoxin is disconnected into the tripeptide unit **2** and the diene fragment **3**. Segment condensation of these fragments and macrolactamization gives the desired macrocycle (Scheme 1).

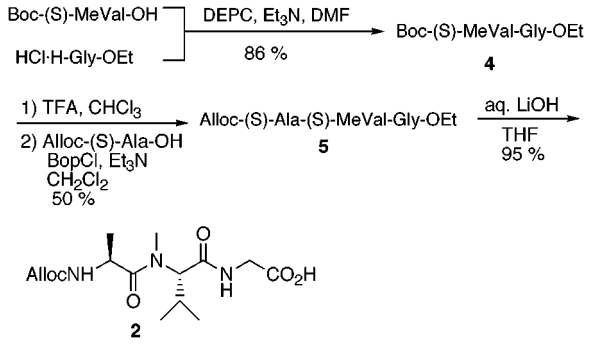
Preparation of the tripepetide unit was achieved in a stepwise manner from glycine ethyl ester as shown in Scheme 2.[3] Coupling of (*S*)-Boc-*N*-methylvaline with the glycine ethyl ester was carried out using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$)[4] to give the dipeptide **4**, $[\alpha]^{26}_D$ −117.7° (*c* 1.0, $CHCl_3$), in 86% yield. After removal of the Boc group from **4** with trifluoroacetic acid (TFA), coupling with (*S*)-Alloc-alanine using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BopCl)[5] afforded the tripeptide **5**, $[\alpha]^{26}_D$ −139.7° (*c* 1.1, $CHCl_3$), in 50% yield. Alkaline saponification of **5** gave the tripeptide unit **2**, which was directly used in the next step after an aqueous workup.

The synthesis of the diene fragment started from 4,4-dimethyl-2-pentyne (**6**)[6] as shown in Scheme 3.[3] After hydroboration of the alkyne **6** with catecholborane, the resulting vinyl borane was coupled with the vinyl iodide **7**[7] under Suzuki-coupling conditions[8] to give the conjugated diene **8** in 53% yield.[9] Oxidation of the allylic alcohol **8** using chemical manganese dioxide (CMD)[10] followed by selective formation of the stereocenters at both C(4) and C(5) by the methodology of Evans et al.[11] produced the alcohol **9**, $[\alpha]^{26}_D$ −21.3° (*c* 1.0, $CHCl_3$), in 93% yield. Removal of the chiral auxiliary from **9** with alkaline hydrogen peroxide and methylation of the resulting carboxylic acid gave the methyl ester **10**, $[\alpha]^{24}_D$ +8.7° (*c* 1.1 $CHCl_3$), in 60% yield. Protection of the secondary hydroxy group of **10** as the triethylsilyl (TES) derivative and reduction of the methyl ester with diisobutylaluminum hydride (DIBAL) provided the primary alcohol **11**, $[\alpha]^{25}_D$ +1.9° (*c* 1.1 MeOH), in 98% yield.[12]

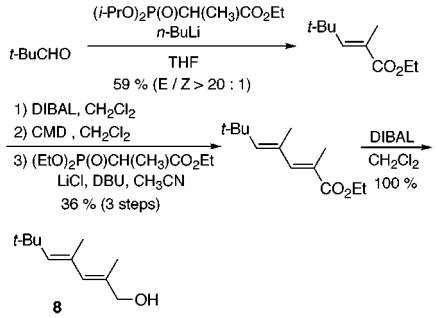
**Scheme 1**




**Scheme 2**




(9) The conjugated diene **8** was also prepared in a stepwise manner using the Horner−Emmons protocol.

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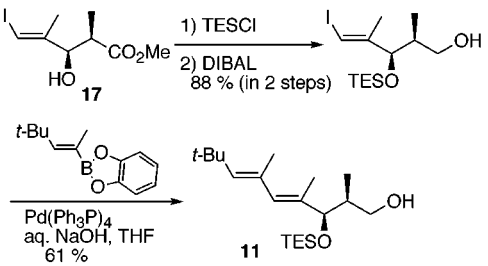
(11) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77−91.

(12) The stereochemistry of the alcohol **11** was confirmed using the known compound **17** (ref 7) as follows.

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(2) For other synthetic studies, see: Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453−1456 and 1457−1460.

(3) Satisfactory spectroscopic data ($^1H$ and $^{13}C$ NMR, IR, HRMS, or elemental analysis) were obtained for all new compounds.

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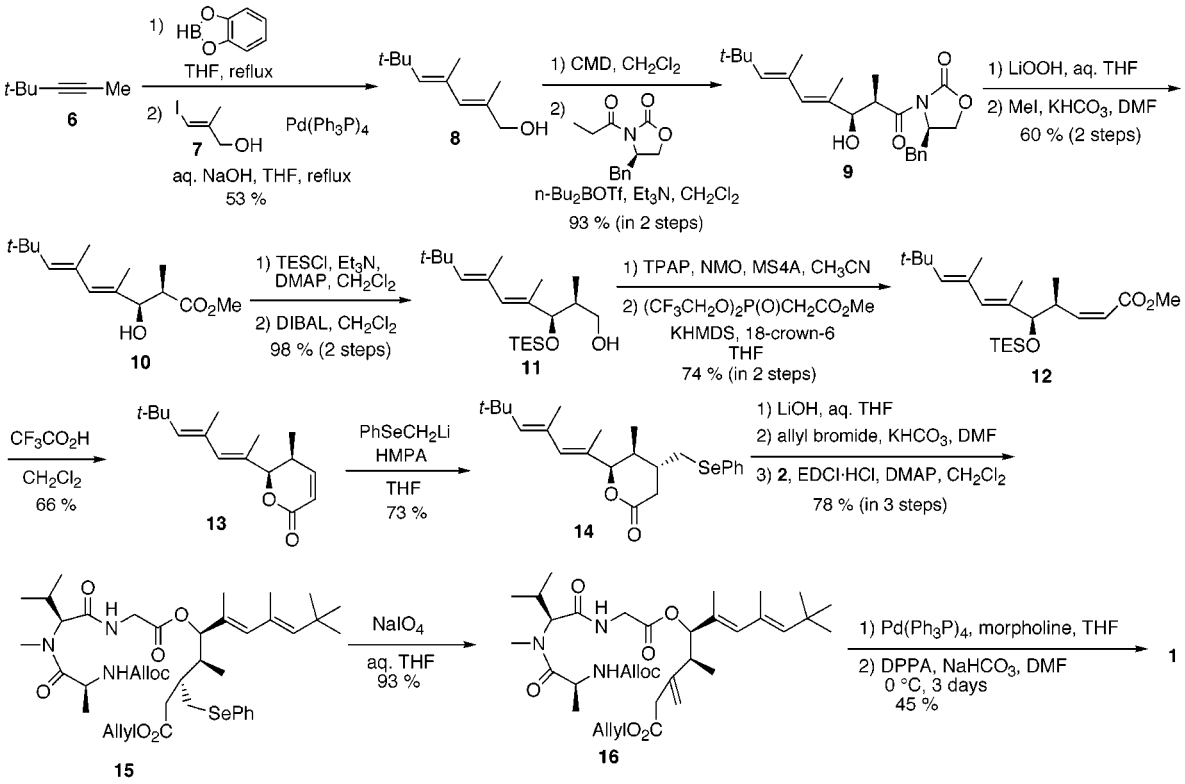
**Scheme 3**




Catalytic oxidation of the alcohol **11** with tetra-*n*-propylammonium perruthenate (TPAP)[13] followed by the Still−Horner olefination[14] afforded the (*Z*)-ester **12**, $[\alpha]^{26}_D$ +86.0° (*c* 1.2, $CHCl_3$), in 74% yield. Cleavage of the secondary TES ether of the (*Z*)-α,*β*-unsaturated ester **12** and acid-catalyzed lactonization simultaneously occurred by treatment with trifluoroacetic acid (TFA) to give the lactone **13**, $[\alpha]^{25}_D$ +357.6° (*c* 0.3, $CHCl_3$), in 66% yield. Stereoselective introduction of the phenylselenomethyl group as a precursor for the isolated terminal olefin to the α,*β*-unsaturated lactone **13** was accomplished using $PhSeCH_2Li$ in the presence of HMPA[15] to provide the selenolactone **14**, mp 80−82 °C, $[\alpha]^{24}_D$ +32.8° (*c* 0.6, $CHCl_3$), in 73% yield as a single isomer.[16] Saponification of the lactone ring **14**, protection of the resulting carboxylic acid as the allyl ester, and segment condensation with a tripeptide unit **2** using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) gave the ester **15**, $[\alpha]^{24}_D$ −79.8° (*c* 0.7, $CHCl_3$), in 78% yield. Oxidative elimination of the phenylselenyl group using $NaIO_4$ afforded the terminal olefin **16**, $[\alpha]^{25}_D$ −77.3° (*c* 0.7, $CHCl_3$), in 93% yield, which is the protected precursor for macrolactamization. Treatment of **16** with $Pd(Ph_3P)_4$ in the presence of morpholine caused simultaneous removal of the C-terminal allyl group and the N-terminal allyloxycarbonyl group, and then the macrolactamization under conditions of high dilution using diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$)[17] and sodium hydrogen carbonate afforded antillatoxin (**1**) in 45% yield.

Although the synthetic antillatoxin showed reasonable $^1H$ and $^{13}C$ NMR spectra and HRMS (EI, obsd $M^+$ *m/z* 503.3362, 0.5 ppm error for $C_{28}H_{45}N_3O_5$), its NMR spectra showed significant differences from those of the natural product. Furthermore, the specific rotation of the synthetic sample ($[\alpha]^{25}_D$ −55.2° (*c* 0.24, MeOH)) was also different from that of the natural product ($[\alpha]_D$ −140° (*c* 0.13, MeOH)).[1] These differences led us to the conclusion that the formula **1** does not accurately reflect the stereostructure for antillatoxin. On the basis of the assumption that the stereochemistries of the amino acids are secure, the stereochemistry at C(4) and C(5) would be doubtful. Further clarification of the relative and absolute configurations at C(4) and C(5) of **1** will be gained by the total synthesis of additional stereoisomers, which are currently underway in our laboratory.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds along with copies of $^1H$ and $^{13}C$ NMR spectra and HRMS spectra of **1** (17 pages).

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