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Total Synthesis and Revision of Absolute Configuration of Antillatoxin, an Ichthyotoxic Cyclic Lipopeptide of Marine Origin

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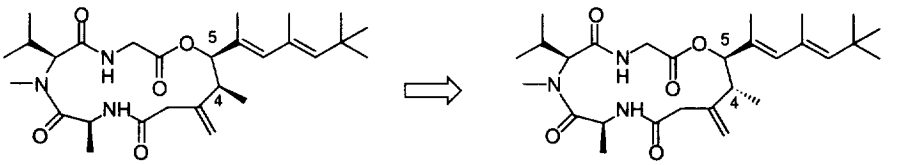
Abstract: The total synthesis of ichthyotoxic cyclic lipopeptide, antillatoxin, isolated from the cyanobacterium *Lyngbya majuscula*, elucidates the stereochemistries at C(4) and C(5) as shown in **1b**, but not **1a**.

Keywords: antillatoxin, ichthyotoxicity, cyclic lipopeptide, total synthesis

The cyclic lipopeptide, antillatoxin (**1**), isolated from the marine cyanobacterium *Lyngbya majuscula* by Gerwick *et al.*,[1] is a highly ichthyotoxic metabolite and has a structure which features a conjugated diene containing the *tert*-butyl group and the isolated terminal olefin. We recently accomplished the total synthesis of (4*S*,5*R*)-antillatoxin having the proposed structure **1a**.[2] However, the ^{1}H and ^{13}C NMR spectra as well as the specific rotation of **1a** synthesized in our laboratory were not identical to those recorded for the naturally derived antillatoxin. Based on the assumption that the stereochemistries of the amino acids are secure, a revision in the assignment of the stereochemistry at C(4) and C(5) is necessitated. Here we describe the total synthesis of antillatoxin and the revision of the proposed structure. We chose the (4*R*,5*R*)-antillatoxin (**1b**) as the next synthetic target, which was proposed as the second possible configuration by the Gerwick group.[1]



(4*S*,5*R*)-Antillatoxin (**1a**) (Proposed)

(4*R*,5*R*)-Antillatoxin (**1b**) (Revised)

The synthesis of (4*R*,5*R*)-antillatoxin (**1b**) was initiated from the diene alcohol **2** prepared according to our previous paper.[2] A stereoselective route to the alcohol **4** from **2** was accomplished using the ester **3** according to the anti-selective boron-mediated asymmetric aldol reaction developed by Abiko and Masamune,[3] followed by protection of the secondary alcohol with the triethylsilyl (TES) group and cleavage of the chiral auxiliary.[4] The alcohol **4** was transformed into the (4*R*,5*R*)-antillatoxin (**1b**) in the same way as developed in our laboratory (Scheme 1).[2] Thus, the TPAP oxidation of **4**, Still's olefination, followed by acidic treatment afforded the α,β-unsaturated lactone **5**, which was transformed into the phenylselenyl derivative **6**. Alkaline cleavage of **6**, allyl esterification, and coupling with the tripeptide **7**[2] produced the ester **8**, which underwent the oxidation to give the linear precursor **9**. Deprotection at the N- and C-terminals followed by macro-

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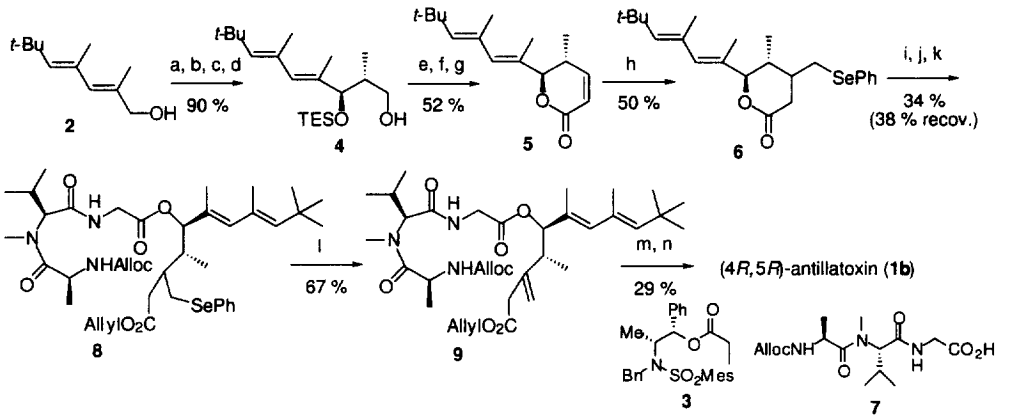
lactamization with DPPA finally produced (4*R*,5*R*)-antillatoxin (**1b**). The ^{1}H and ^{13}C NMR spectra as well as the specific rotation of our synthetic sample were completely identical with those published for the natural product.



Scheme 1. Synthesis of **1b**. a) CMD, CH_2Cl_2; b) **3**, (*c*-Hex)$_2$BOTf, Et_3N, CH_2Cl_2; c) TESOTf, 2,6-lutidine, $CHCl_3$; d) DIBAL, CH_2Cl_2; e) TPAP, NMO, MS4A, CH_3CN; f) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF; g) TFA, CH_2Cl_2; h) $PhSeCH_2Li$, HMPA, THF; i) LiOH, aq. THF; j) allyl bromide, $KHCO_3$, DMF; k) **7**, EDCI·HCl, DMAP, CH_2Cl_2; l) $NaIO_4$, aq. THF; m) $Pd(Ph_3P)_4$, morpholine, THF; n) DPPA, $NaHCO_3$, DMF.
CMD = chemical manganese dioxide, TESOTf = triethylsilyl trifluoromethanesulfonate, DIBAL = diisobutylaluminum hydride, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide, HMDS = hexamethyldisilazane, TFA = trifluoroacetic acid, HMPA = hexamethylphosphoramide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP = 4-(dimethylamino)pyridine, DPPA = diphenyl phosphorazidate, Bn = benzyl, Mes = mesitylenesulfonyl, Alloc = allyloxycarbonyl

As a consequence of our synthetic studies, we accomplished the first total synthesis of antillatoxin and clearly demonstrated that the real structure of antillatoxin should be revised to have the 4*R*,5*R* configuration. The total synthesis of further additional stereoisomers and their biological evaluation will be reported in due course.

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References and Notes

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3. Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586-2587.
4. The absolute stereochemistry of the alcohol **4** was further confirmed as follows.