Synthesis of Epiantillatoxin, a Stereoisomer of the Potent Ichthyotoxin from *Lyngbya majuscula*

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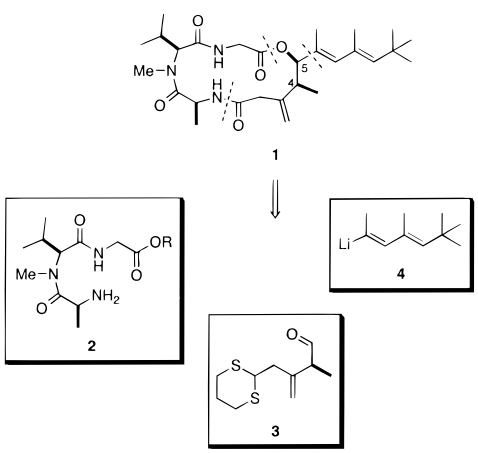
Received September 18, 1998

Cyanobacteria (blue-green algae) have proven to be a rich source of novel marine metabolites.[1] A collection of *Lyngbya majuscula* near Curaçao furnished, in addition to the novel tubulin-binding agent curacin A,[2] a small amount of a powerful ichthyotoxic substance named antillatoxin (LD_{50} = 0.005 mg/mL). Structure **1**, including the (4*S*,5*R*) configuration, was attributed to antillatoxin by Gerwick et al. on the basis of ^{1}H NMR spectroscopy, analysis of its CD spectrum, and molecular modeling.[3] Herein, we report a synthesis of **1** which establishes that this assignment to antillatoxin is incorrect.[4]

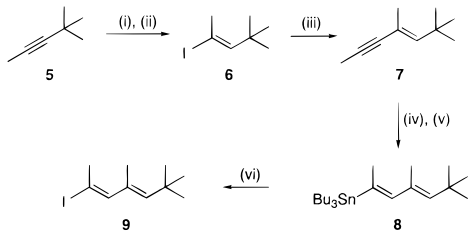
Our synthetic approach follows a convergent strategy which assembles **1** from the tripeptide **2**, an aldehyde **3**, and 1,3,5,5-tetramethylhexa-1,3-dienyllithium (**4**). After the C5−C6 bond is



established, the coupled product is connected to the carboxyl terminus of **2** prior to final lactamization.[5]

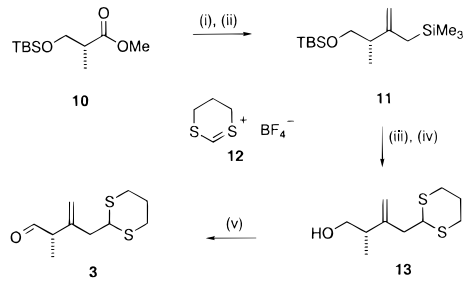
Synthesis of the diene side chain **4** of antillatoxin began from 4,4-dimethylpent-2-yne (**5**), which was subjected to hydrozirconation with Schwartz' reagent[6] and the resultant vinylzirconocene species was reacted with *N*-iodosuccinimide to yield iodoalkene **6**.[7] The latter was coupled with propynylmagnesium bromide in the presence of a palladium(0) catalyst[8] to give **7**. Stannylcupration of enyne **7** at low temperature, followed by methanolysis, led to **8**, accompanied by ca. 10% of the inseparable regioisomeric dienylstannane.[9] Iodination of the mixture furnished pure iododiene **9** after flash chromatography (see Scheme 1).

Scheme 1[a]



[a] (i) Cp_2ZrClH, THF; (ii) *N*-iodosuccinimide; (iii) MeC≡CMgBr, $Pd(PPh_3)_4$ (2.5 mol %), THF, 68% from **5**; (iv) $Bu_3Sn(Bu)CuCNLi_2$, THF, −50 °C; (v) MeOH, −50 °C → −10 °C, overnight; (vi) I_2, Et_2O, 0 °C, 52% from **7**.

Scheme 2[a]



[a] (i) Me_3SiCH_2MgCl, $CeCl_3$, THF; (ii) SiO_2, CH_2Cl_2, 99%; (iii) **12**, CH_3NO_2, 0 °C; (iv) BF_3·OEt_2, 0 °C, 70%; (v) IBX (1 M in DMSO), THF, 70%.

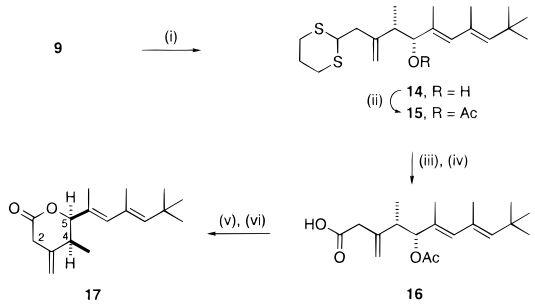
The C1−C5 subunit **3** of **1** was constructed from methyl (*R*)-3-hydroxy-2-methylpropionate via a sequence which conveniently differentiated the two aldehyde termini of this segment. Addition of excess (trimethylsilyl)methylmagnesium chloride to **10** in the presence of cerium trichloride gave a tertiary carbinol which, upon exposure to silica, underwent Peterson elimination to furnish allylsilane **11**.[10] Electrophilic substitution of **11** with 1,3-dithienium fluoroborate (**12**)[11] in nitromethane produced a mixture of alcohol **13** and its TBS ether (ca. 1:1); the mixture was converted directly to **13** upon treatment with boron trifluoride etherate (see Scheme 2). Oxidation of **13** with *o*-iodoxybenzoic acid (IBX)[12] furnished the unstable aldehyde **3** which was reacted immediately with the lithiated diene **4**, obtained from **9** by treatment with *tert*-butyllithium at low temperature, to yield an 8:1 mixture of two stereoisomeric alcohols. After chromatographic purification, the major alcohol **14** was acetylated, and the acetate **15** was converted to carboxylic acid **16** by mild cleavage of the dithiane[13] followed by oxidation of the resultant aldehyde with buffered sodium chlorite. The relative configuration of **16** was established by its transformation to δ-lactone **17** in which the cis relationship of hydrogens at C4 and C5 was confirmed by their coupling constant of 3.0 Hz and a NOE of 7%. This result established the configuration of the major alcohol from the reaction of **3** with **9** as (5*R*), corresponding to the Felkin mode of addition (see Scheme 3).

The tripeptide unit of antillatoxin was prepared from Cbz-protected *N*-methylvaline (**18**)[14] by bromotris(dimethylamino)-phosphonium hexafluorophosphate(BroP)-mediated coupling with methyl glycinate to give dipeptide **19**. The Cbz group of **19** was

(1) Moore, R. E. *J. Ind. Microbiol.* **1996**, *17*, 134.
(2) (a) Nagle, D. G.; Geralds, R. S.; Yoo, H.-D.; Gerwick, W. H.; Kim, T.-S.; Nambu, M.; White, J. D. *Tetrahedron Lett.* **1995**, *36*, 1189. (b) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612. (c) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc*. **1997,** *119*, 103.
(3) Orjala, J.; Nagle, D. G.; Hsu, V. L.; Gerwick, W. H. *J. Am. Chem. Soc*. **1995**, *117*, 8281.
(4) The same conclusion was reached independently by Yokokawa and Shioiri (Yokokawa, F.; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 8638).
(5) An unsuccessful approach to **1** along different lines has been reported (Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453, 1457).
(6) Takahashi, T.; Suzuki, N. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, U.K., 1995; Vol. 2, pp 1082−1087.
(7) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1.
(8) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett*. **1978**, 191.
(9) Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, 47, 1163.
(10) Lee, T. V.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F. S.; Yeoh, H. T.-L. *Tetrahedron* **1989**, *45*, 5877.
(11) Westerlund, C. *Tetrahedron Lett.* **1982**, *23*, 4835.
(12) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem*. **1996**, *61*, 9272.
(13) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68.
(14) McDermott, J. R.; Benoiton, N. L. *Can J. Chem*. **1973**, *51*, 1915.

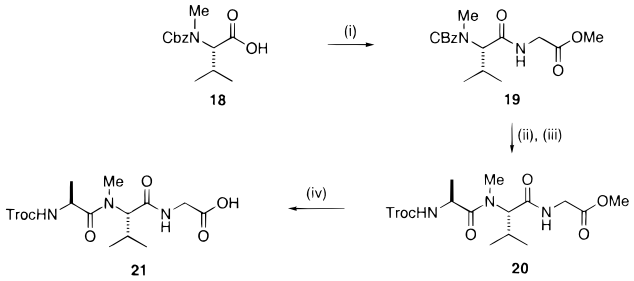
10.1021/ja983334l CCC: $18.00
Published on Web 01/22/1999

Scheme 3[a]



[a] (i) *t*-BuLi, THF, −78 °C, 20 min, then **3**, 60%; (ii) Ac_2O, py, 20 h, 100%; (iii) MeI, $CaCO_3$, MeCN−H_2O, 16 h; (iv) $NaClO_2$, NaH_2PO_4, MeCH═CMe_2, *t*-BuOH−H_2O, 91%; (v) K_2CO_3, MeOH; (vi) CSA, CH_2Cl_2, 43%.

Scheme 4[a]



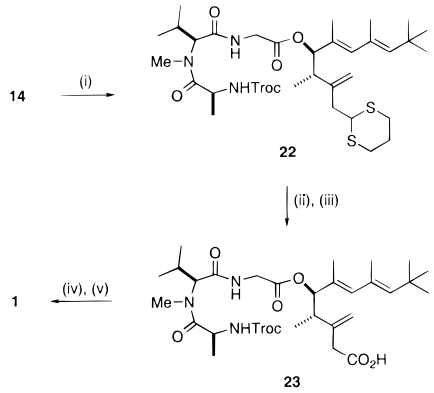
[a] (i) Gly·OMe, BroP, (*i*-Pr)$_2$ NEt, CH_2Cl_2, 93%; (ii) H_2, Pd/C, MeOH; (iii)Troc·ala OH, HATU, (*i*-Pr)$_2$NEt, CH_2Cl_2, 74%; (iv) LiOH, THF, 100%.

removed by hydrogenolysis, and the amine was condensed, using (*O*-7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as the coupling agent, with 1,1,1-trichloroethoxycarbonyl (Troc)-protected alanine.[15] The resultant tripeptide **20** was saponified to furnish carboxylic acid **21** (see Scheme 4). Esterification of **14** with **21** was carried out in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and afforded **22** in good yield. After removal of the dithiane, the derived aldehyde was oxidized to carboxylic acid **23**. The Troc-protecting group was cleaved, and final macrolactamization of the liberated amino acid using HATU produced **1** (see Scheme 5). The latter was not identical in spectral properties, optical rotation, or chromatographic behavior with a sample of natural antillatoxin, and it is therefore concluded that the structure assigned[3] to antillatoxin must be revised.

Although most features of the ^{1}H and ^{13}C NMR spectra of our synthetic **1** are similar to those of natural antillatoxin and are

(15) Carson, J. F. *Synthesis* **1981**, 268.

Scheme 5[a]



[a] (i) **21**, EDC, DMAP, CH_2Cl_2; (ii) MeI, $CaCO_3$, MeCN−H_2O; (iii) $NaClO_2$, NaH_2PO_4, MeCH═CMe_2, *t*-BuOH−H_2O, 75% from **14**; (iv) Zn, KH_2PO_4, THF; (v) HATU, (*i*-Pr)$_2$ NEt, DMF, 60% from **23**.

consistent with a stereoisomeric relationship, conspicuous differences are the chemical shift of H4 (δ 2.71 in **1**, δ 2.17 in antillatoxin) and the coupling constant between H4 and H5. The observed value of this coupling in **1** ($J \approx 0$ Hz) is indicative of a cis orientation of hydrogens, whereas the reported value ($J =$ 11 Hz) for antillatoxin clearly is not. Cis configuration at C4,C5 in the natural product was assigned by Gerwick on the basis of a NOE between protons attached to these carbons,[3] but reexamination of the NOE experiment has found that this result is spurious.[16] NMR evidence therefore points strongly toward a 4,5-*trans* configuration for antillatoxin. At this time, we are unable to distinguish between the (4*R*,5*R*) and (4*S*,5*S*) stereochemical assignments for the natural product.

Acknowledgment. We thank Professor William H. Gerwick, College of Pharmacy, Oregon State University, for NMR spectra of natural antillatoxin and for comparison of our synthetic **1** with a natural sample. Financial support was provided by the National Institutes of Health (GM50574), by the Marine-Freshwater Biomedical Sciences Center of Oregon State University (ES03850), and by Dupont Pharmaceutical Company.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra (^{1}H and ^{13}C) for synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA983334L

(16) Private communication from Professor William H. Gerwick.