Synthesis of Curacin A: A Powerful Antimitotic from the Cyanobacterium *Lyngbya majuscula*

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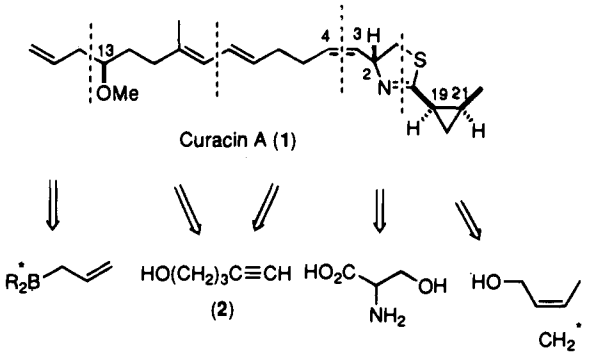
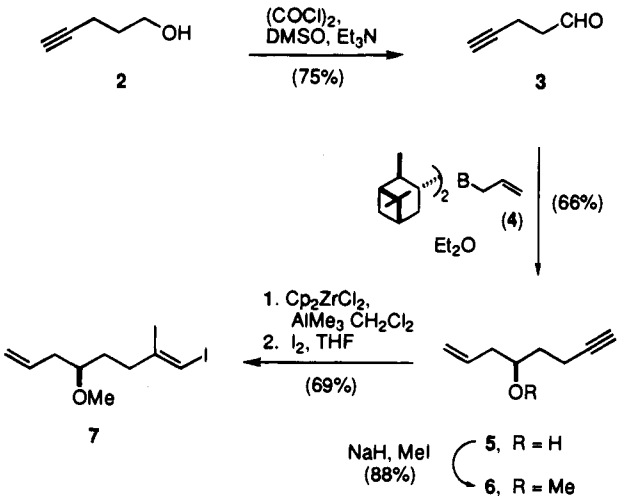
The cyanobacterium *Lyngbya majuscula* produces a cyclopropane-containing lipid curacin A (**1**) with potent antimitotic activity.[1] Studies of the biological properties of **1** have revealed that it binds with high affinity to the colchicine site of tubulin and exerts its antiproliferative action at the cellular level by inhibiting the polymerization of tubulin.[2] The structure initially deduced for curacin A by Gerwick et al.[1] was devoid of stereochemistry except for assignment of *E,E* geometry to the conjugated diene and *cis* relative configuration at the cyclopropane. We now describe an asymmetric synthesis of curacin A (**1**) which confirms the geometry attributed to the double bonds and cyclopropane and which establishes its absolute configuration as (2*R*,13*R*,19*R*,21*S*).[3] The synthesis assembles **1** in linear fashion from five subunits, two of which are derived from 4-pentyn-1-ol (**2**). The strategic disconnections around which the synthesis is designed are shown in Scheme 1.

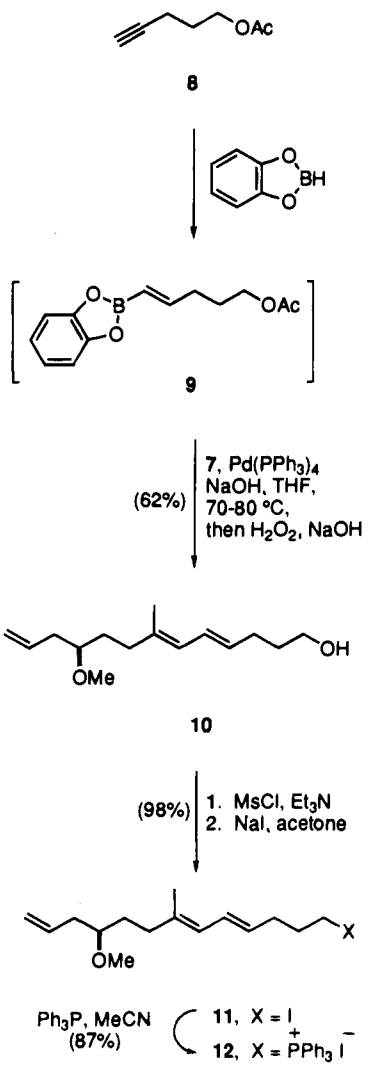
Scheme 1



Swern oxidation of **2**,[4] followed by allylation of the resultant pentynal **3** with the salt-free borane **4** derived from (−)-*B*-methoxydiisopinocampheylborane,[5] gave (*R*)-**5** in 95% ee as determined from the ^1H and ^{19}F NMR spectra of its Mosher ester.[6] The alcohol **5** was converted to its methyl ether **6**, which was subjected to Negishi's zirconation–iodination conditions[7] to give the (*E*)-iodooctadiene derivative **7**. In a parallel



sequence, **2** was acetylated and the alkyne **8** was treated with catecholborane to yield the vinylboronate **9**. *In situ* Suzuki



coupling[8] of **9** with the iodoalkene **7** in the presence of tetrakis(triphenylphosphine)palladium as catalyst afforded **10** in which the conjugated diene unit was produced with clean *E,E* geometry. Alcohol **10** was converted via its mesylate to the

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(2) Hamel, E.; Blokhin, A. V.; Nagle, D. G.; Yoo, H.-D.; Gerwick, W. H. *Drug Dev. Res.*, in press.
(3) Degradative studies carried out on curacin A have reached this conclusion independently (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).
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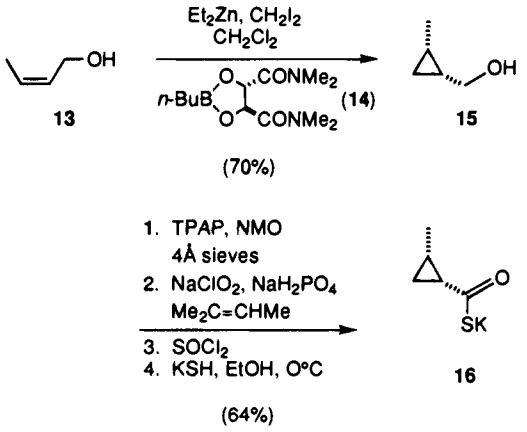
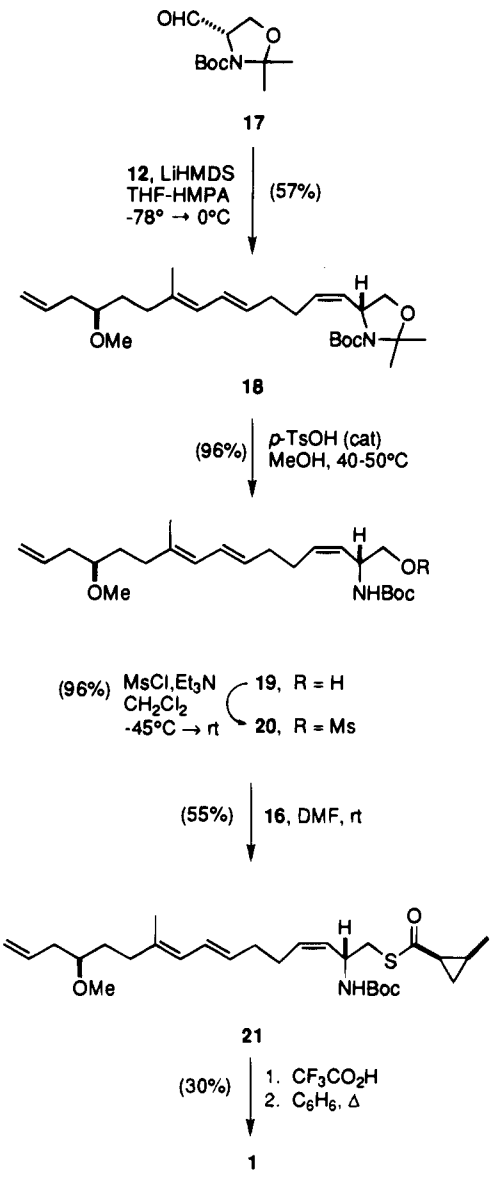
iodo derivative **11**, which was advanced to phosphonium salt **12** upon treatment with triphenylphosphine in acetonitrile.

Asymmetric synthesis of the cyclopropane moiety of **1** was carried out using the method recently reported by Charette.[9] Thus, treatment of *cis*-crotyl alcohol (**13**), prepared in 83% yield by hydrogenation of 2-butyn-1-ol over Lindlar's catalyst, with diiodomethane in the presence of diethylzinc and the *n*-butylboron complex of (*S,S*)-(−)-*N,N,N′,N′*-tetramethyltartaramide (**14**) gave **15** in >95% ee, as determined by ^{1}H NMR analysis of its Mosher ester.[6] Oxidation of **15** with perruthenate[10] afforded the cyclopropanecarboxaldehyde, which was immediately oxidized further with sodium chlorite[11] to furnish (1*R*,2*S*)-2-methylcyclopropanecarboxylic acid. The latter was converted to its potassium thiocarboxylate **16** by treatment of the derived acyl chloride with potassium hydrogen sulfide.[12]



The thiazoline unit of **1** was incorporated into the synthetic route via oxazolidine **17**,[13] prepared from (*S*)-serine. Wittig reaction of **17** with the phosphorane derived from **12** by treatment with lithium hexamethyldisilazide cleanly afforded tetraene **18** with no trace of the *trans* $\Delta^{3,4}$ isomer. Cleavage of the acetonide protection from **18** furnished alcohol **19**, which was converted to its mesylate **20**, and the latter was coupled to **16** to yield thioester **21**. Removal of the Boc group, followed by exposure of the resulting amine to refluxing benzene, gave curacin A (**1**), identical by comparison of chromatographic behavior (HPLC, Versapack column, 4% ethyl acetate in hexane) and spectroscopic data (^{1}H NMR, GC−MS and circular dichroism) with a sample of natural material. Curacin A is unstable and is best preserved as a frozen solution in benzene.



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Supplementary Material Available: Characterization data for **5**−**8**, **10**−**12**, **15**, **18**, **19**, and **21** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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