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A Concise Total Synthesis of (+)-Curacin A, a Novel Cyclopropyl-substituted Thiazoline from the Cyanobacterium *Lyngbya majuscula*

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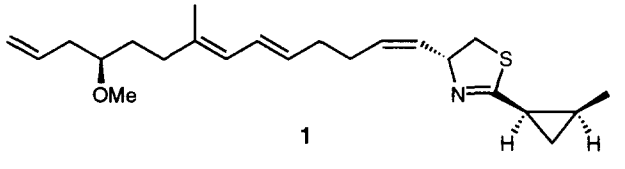
Abstract: A total synthesis of (+)-curacin A **1** which features a facile and selective thioacylation of the polyene amino-alcohol **2** with the benzotriazole-derived cyclopropyl thioamide **3**, leading to **15**, as a key step is described.

Curacin A **1** is a potent antimitotic agent isolated from the cyanobacterium *Lyngbya majuscula* collected off the coast of Curaçao.[1] The molecule also exhibits mammalian cell antiproliferative activity (IC_{50} 6.8 ng/mL) and studies have shown this is associated with its capacity to inhibit tubulin polymerisation at the colchicine site.[2] Curacin A has an unusual structure which incorporates a novel 2-cyclopropyl-4-alkenyl substituted thiazoline unit as a key feature. In view of its novel structure and interesting biological activity, its total synthesis has attracted a significant amount of attention.[3] Previous synthetic efforts towards curacin A have differed largely according to the strategy adopted to the chiral thiazoline moiety in the molecule.[4] Our own approach is not different in this respect, but here we describe a new strategy to the 2-cyclopropyl-4-alkenyl substituted thiazoline unit in curacin A which features the facile and selective thioacylation of the amino-alcohol **2** with the benzotriazole derived thioamide **3**, as the key step.[5]



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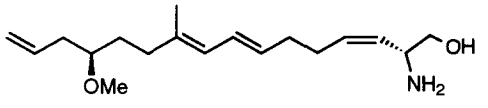

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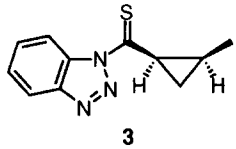

3

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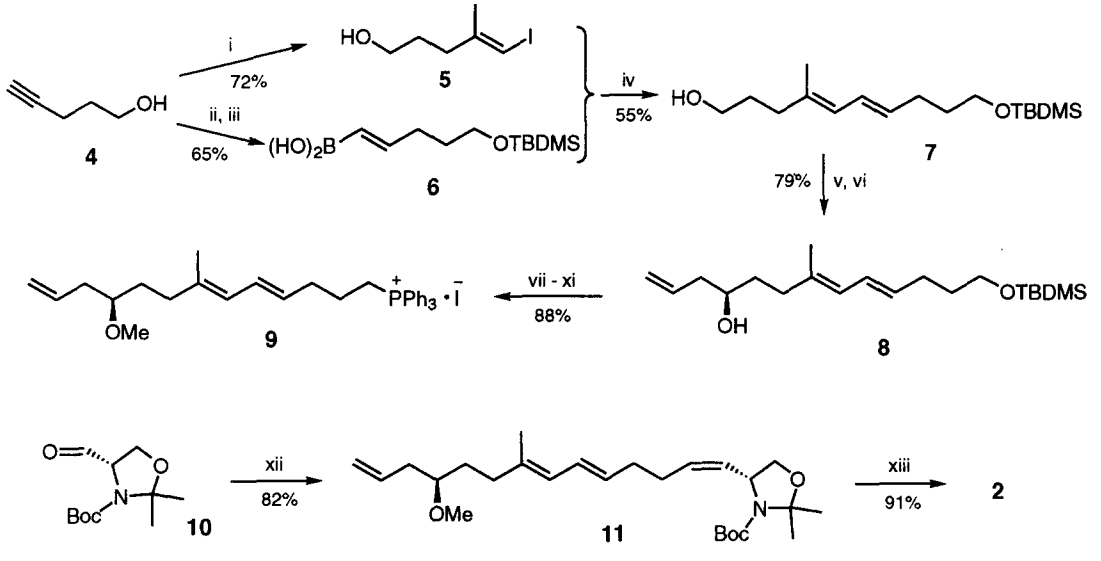
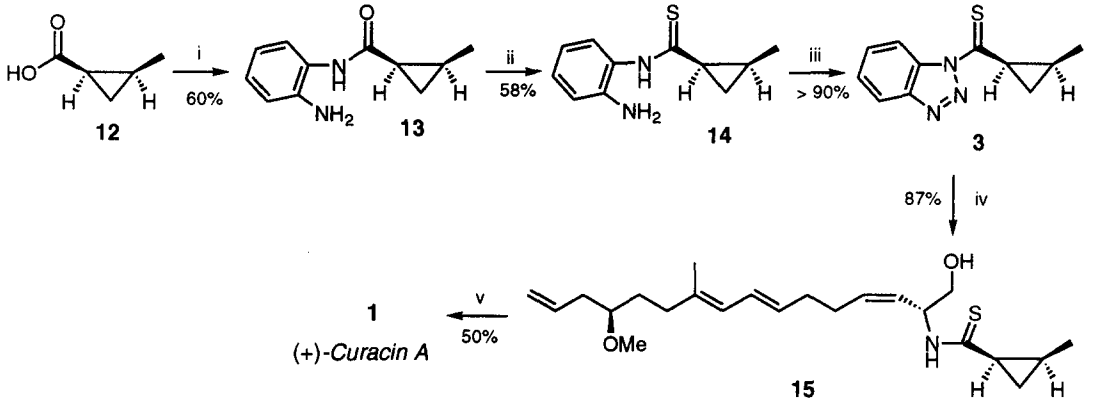
Thus, the phosphonium salt precursor **7** of the polyene portion of curacin A was first elaborated starting from 4-pentyn-1-ol as illustrated in Scheme 1. Carbozirconation[6] of 4-pentyn-1-ol **4** followed by iodination led to the *E*-vinyl iodide **5**, which by Suzuki coupling[7] to the vinylboronic acid **6** derived from the TBDMS ether of **4**, then produced the *E,E*-diene **7**.[8] Oxidation of **7**, followed by allylboronation of the resulting aldehyde with the allylborane derived from (-)-B-methoxydiisopinocampheylborane,[9] next led to the carbinol (**8**; > 96% ee by Mosher ester analysis). The triene alcohol **8**, was then converted into the known phosphonium salt **9**[3] following O-methylation, cleavage of the silyl ether, mesylation, elaboration of the corresponding iodide and treatment with triphenylphosphine. A *Z*-selective Wittig reaction between Garner's aldehyde **10**[10] and the ylide derived from **9** in the presence of sodium hexamethyldisilazide in THF (-78 °C to 0 °C) next produced the *Z,E,E*-tetraene **11**[3] cleanly and in 82% yield, which was then hydrolysed to the amino-alcohol **2** using 10% HCl in MeOH at 40 °C (Scheme 1).



Reagents: i, Me_3Al, Cp_2ZrCl_2, I_2; ii, TBDMSCl, Et_3N, DMAP, CH_2Cl_2; iii, Catecholborane, H_2O; iv, $Pd(PPh_3)_4$, TlOH; v, Dess-Martin periodinane; vi, (-)-*B*-allyl isopinocampheylborane; MeOH, NaOH, H_2O_2; vii, NaH, MeI, THF; viii, TBAF, THF; ix, MsCl, Et_3N; x, NaI, acetone; xi, PPh_3, CH_3CN; xii, **9**, NaHMDS, - 78 °C - 0 °C, THF; xiii, 10% HCl, MeOH, 40 °C.

Scheme 1

Having investigated a range of thioacylation reagents derived from (+)-2-methylcyclopropanecarboxylic acid **12**[11] in order to convert the amino-alcohol **2** into the penultimate precursor, *ie* **15**, to curacin A, we decided to use the benzotriazole derived thioamide **3**.[12] All of the other thioacylation reagents we examined[13] resulted largely in the formation of products produced as a result of simultaneous cyclopropane ring opening in the precursors or products. The benzotriazole cyclopropyl thioamide **3** was conveniently derived from (+)-2-methylcyclopropanecarboxylic acid **12** following amide **13** formation with 1,2-diaminobenzene, thionation, and diazotization of the resulting thioamide **14**. When the amino-alcohol **2** was added to a solution of **3** in DMF at 0 °C it was converted into the polyene substituted thioamide **15** in 87% yield. Finally, cyclodehydration of **15**



Reagents: i, 1,2-Phenylenediamine, pyBOP, Et_3N; ii, P_4S_{10}, Na_2CO_3; iii, $NaNO_2$, $AcOH/H_2O$; iv, **2**, DMF, 0 °C; v, Burgess' reagent, THF.

Scheme 2

using Burgess' reagent[14] gave (+)-curacin A **1** as a colourless viscous oil, $[\alpha]_D^{21}$ + 61.3 (c 0.75, $CHCl_3$), in 50% yield (Scheme 2). The synthetic curacin A showed pmr and cmr data, together with optical rotation data, lit $[\alpha]_D^{20}$ + 62.0 (c 1.1, $CHCl_3$), which were identical to those recorded for natural curacin A from *L. majuscula.*

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