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# Synthesis of Curacin A, An Antimitotic Cyclopropane-Thiazoline From The Marine Cyanobacterium *Lyngbya majuscula*

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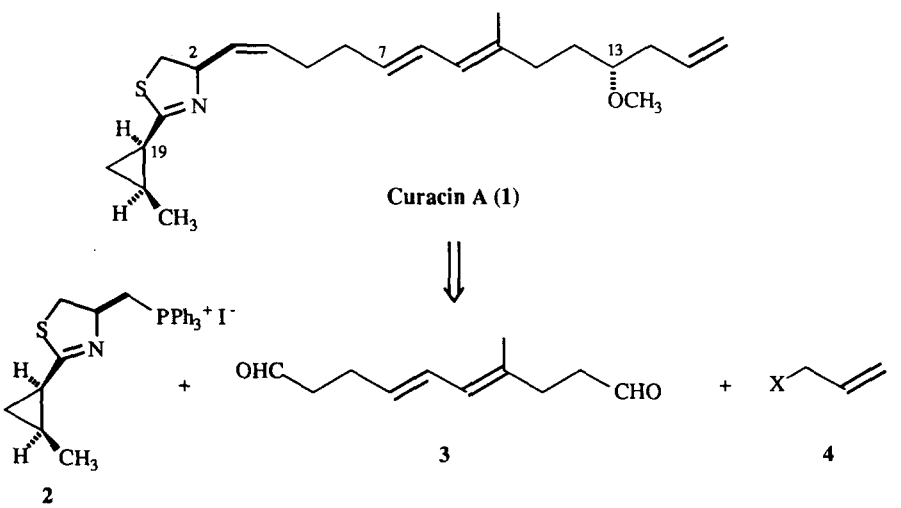
**Abstract:** Charette asymmetric cyclopropanation, chiral thiazoline synthesis by thioamide cyclization under modified Mitsunobu conditions, Ti(*i*PrO)$_4$/bi-naphthol catalyzed allylstannane addition, and an exceptionally mild two-carbon homologation via dehydrative alkylation with phenylsulfonylacetonitrile/$Ph_3P$/ADDP convened in an efficient, stereocontrolled route to the title bioactive heterocycle. Copyright © 1996 Elsevier Science Ltd

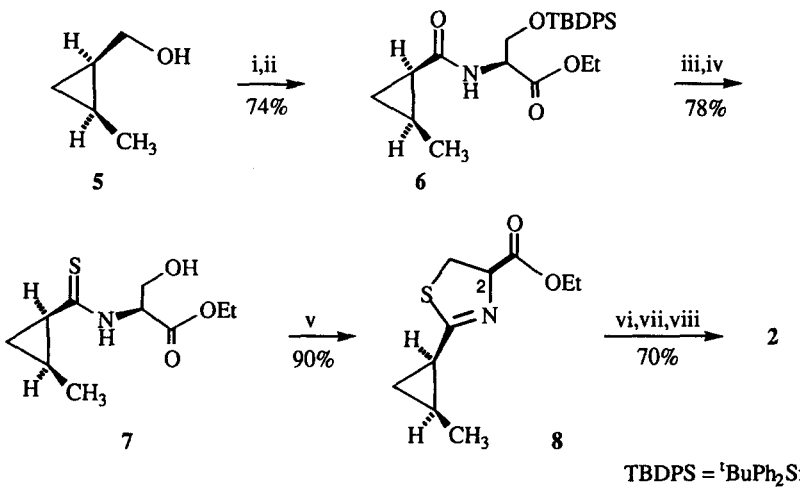
Curacin A[1] (**1**) is the most prominent member of a small family[2] of potent antimitotic lipids elaborated by the Caribbean cyanobacterium *Lyngbya majuscula*. It exerts its antiproliferative effects by inhibiting microtubule assembly through high affinity association with the colchicine-binding domain, despite any perceivable topographic similarity with the latter alkaloid.[3] The structure of **1** was established by degradative studies[4,5] as well as total synthesis.[6,7] The novel cyclopropane-thiazoline moiety, characteristic of this group of marine natural products, appears necessary but not sufficient for repressing tubulin polymerization.[4] To expedite current pharmacologic testing, we report herein an efficient, asymmetric synthesis of **1** based on a convergent strategy (Scheme 1) which unites Wittig salt **2**, containing three of the target's four chiral centers, with a differentiated form of bis-aldehyde **3**. The fourth center at C(13) was created by the stereocontrolled addition of an allylic unit **4** to the remaining aldehyde.

**Scheme 1**



To prepare the lefthand moiety, the known[6a] chiral cyclopropylmethanol **5** (95% ee), made by Charette asymmetric cyclopropanation[8] of *cis*-2-buten-1-ol, was subjected to catalytic $RuCl_3$ oxidation followed by DCC mediated condensation with the *tert*-butyldiphenylsilyl (TBDPS) ether of L-serine ethyl ester (**9**) to give amide **6** (Scheme 2). Thionation of **6** using Lawesson's reagent smoothly generated the corresponding thioamide from which alcohol **7** was obtained by fluoride induced desilylation. This result stands in stark contrast to the reported failure of Lawesson's reagent and derivatives with a closely related amide[6b] containing the C(7)-C(10) diene and may be another manifestation the diene's unusual lability (*vide infra*). Closure of **7** to thiazoline **8**[9] using Burgess' salt as recommended[10] proved disappointing; thiazoline **8** was isolated in modest yield (56%) accompanied by an unidentified by-product (30-38%). In contrast, cyclization under modified Mitsunobu conditions[11,12] at -20°C furnished **8** (90%) and its chromatographically separable C(2)-epimer (4%). $Zn(BH_4)_2$ reduction of **8** in $Et_2O$ proceeded smoothly and completely avoided the epimerization at C(2) observed with other reagents.[13] Conventional tosylation of the resultant alcohol and displacement using excess $Ph_3P$ led to Wittig salt **2** in good overall yield.

**Scheme 2**

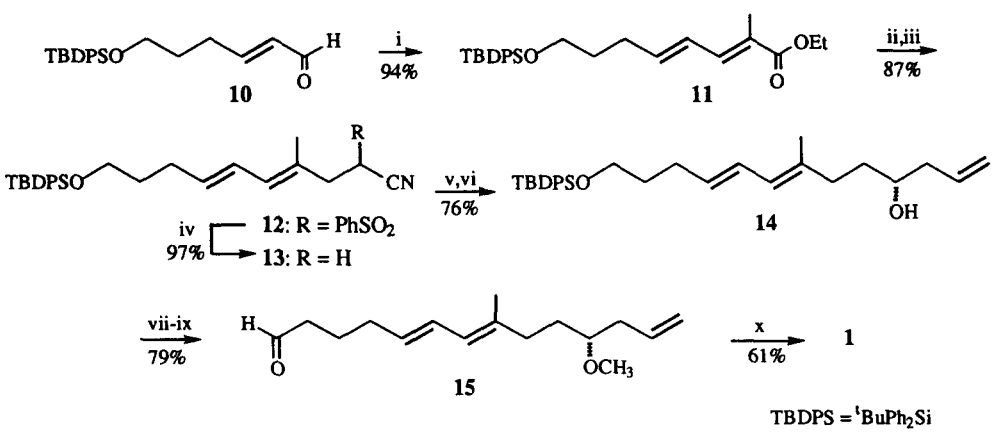



(i) $RuCl_3/NaIO_4$, $CCl_4/CH_3CN/H_2O$, (1:1:1.5), 23°C, 2 h; (ii) **9**, DCC, DMAP, $CH_3CN$ 23°C, 12 h; (iii) Lawesson's reagent (0.6 equiv), $PhCH_3$, 90°C, 5 h; (iv) *n*-$Bu_4NF$, THF 23°C, 2 h; (v) $Me_3P$ (2 equiv)/ADDP (1.3 equiv), $PhCH_3$, -45° to -20°C, 2 h; (vi) $Zn(BH_4)_2$, $Et_2O$, 23°C, 2 h; (vii) TsCl, $Et_3N$, $CH_3CN$, 23°C, 12 h; (viii) $PPh_3$, NaI, $CH_3CN$, 90°C, 12 h.

The central section representing C(4)-C(13) was crafted from aldehyde **10**[14] by homologation to all-trans ester **11** (94%) utilizing commercial (carbethoxyethylidene)triphenylphosphorane (**16**) (Scheme 3). A small amount (~4%) of contaminating 7E,9Z-diene was removed chromatographically: TLC ($SiO_2$) hexanes/$CH_2Cl_2$ 1:1, $R_f$ ~ 0.34 and 0.43, respectively. Efforts to achieve a second two-carbon extension following DIBAL-H reduction (95%) of **11** were thwarted . Electrophilic derivatives of the resultant allylic alcohol (e.g., mesylate, tosylate, chloride, bromide) could not be isolated and/or underwent extensive elimination when exposed to

nucleophiles such as the lithium salt of *tert*-butyl acetate. On the other hand, dehydrative alkylation at room temperature using phenylsulfonylacetonitrile/$Ph_3P$/ADDP as recently described by our laboratory[15] gave rise to cyanosulfone **12** in excellent yield. The phenylsulfonyl group was easily stripped away[15] by Mg/$HgCl_2$ in MeOH leaving nitrile **13**. Low temperature DIBAL-H treatment led to the corresponding aldehyde from which alcohol **14** was secured by stereocontrolled allylation (>95% ee) using Ti(*i*PrO)$_4$/(S)-bi-naphthol according to Keck et al.[16] Serial methylation of the free alcohol, desilylation, and catalytic TPAP oxidation furnished aldehyde **15**. Wittig olefination between **2** and **15** completed the synthesis of **1**, which was identical by $^1H/^{13}C$ NMR, HPLC, and optical rotation with a sample of natural material generously provided by Prof. Wm. Gerwick (Oregon State University).

**Scheme 3**




(i) **16**, $CH_2Cl_2$, 23°C, 3 h; (ii) *i*-$Bu_2AlH$, $PhCH_3$, -78°C, 1 h; (iii) $PhSO_2CH_2CN/PPh_3$/ADDP (2 equiv each), PhH, 23°C, 18 h; (iv) Mg/$HgCl_2$, MeOH/THF (1:1), 0°C, 2 h; (v) *i*-$Bu_2AlH$, $PhCH_3$, -78°C, 1 h; (vi) *n*-$Bu_3SnCH_2CH{=}CH_2$, (S)-1,1'-bi-2-naphthol, Ti(iPrO)$_4$ (15 mol %), 4Å molecular sieves, $CH_2Cl_2$, -20°C, 3 d; (vii) NaH, MeI, THF, 23°C, 12 h; (viii) *n*-$Bu_4NF$, THF, 23°C, 2 h; (ix) *n*-$Pr_4NRuO_4$/NMO, 4Å molecular sieves, $CH_2Cl_2$, -23°C, 0.5 h; (x) , $KN(TMS)_2$, THF, -20°C, 1 h; **15**, -78° to 23°C.

In summary, we have described a facile, stereocontrolled synthesis of curacin A (**1**) in good overall yield. Implicit in this strategy is ready access to structural analogs of interest in elucidating the structure-activity relationships in this family of promising anticancer agents. Details of this work will be published elsewhere.

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9. Physical and spectral data for **8**: $^1$H NMR (CDCl , 250 MHz) δ 4.98 (dd, 1H, J = 9.0, 9.6 Hz), 4.27 (q, 2H, J = 7.1 Hz), 3.51 (d, 2H, J = 9.5 Hz), 1.92 (ddd, 1H, J = 6.0,8.4, 8.4 Hz), 1.41-1.23 (m, 1H), 1.32 (t, 3H, J = 7.1 Hz), 1.17-1.05 (m, 1H), 1.11 (d, 3H, J = 6.1 Hz), 1.04-0.95 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 173.51, 171.12, 77.84, 61.60, 35.71, 19.86, 15.65, 14.35, 14.14, 12.47; $[\alpha]^{23}_D$ 52.1° (c 0.92, EtOH). Compound **15**: $^1$H NMR ($CDCl_3$, 250 MHz) δ 9.78 (t, 1H, J = 1.8 Hz), 6.23 (dd, 1H, J = 10.7, 15.0 Hz), 5.79 (d, 1H, J = 10.7 Hz), 5.59 (dt, 1H, J = 7.2, 15.1 Hz), 3.67 (t, 2H, J = 6.3 Hz), 2.56 (t, 2H, J = 7.2 Hz), 2.37 (t, 2H, J = 7.5 Hz), 2.20 (q, 2H, J = 7.3 Hz), 1.73 (s, 3H), 1.65 (q, 2H, J = 6.9 Hz), 1.05 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 202.27, 135.58, 134.06, 133.77, 133.06, 129.52, 127.59, 126.54, 125.58, 63.23, 42.09, 32.44, 31.89, 29.19, 26.86, 19.25, 16.60.
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