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ASYMMETRIC TOTAL SYNTHESIS OF CURACIN A

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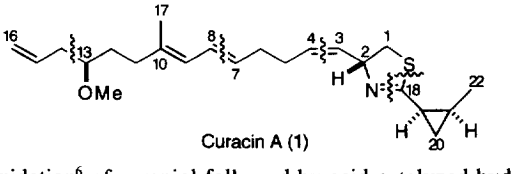
Abstract: Curacin A (**1**), a novel antimitotic agent, was synthesized in a highly stereo-controlled manner. The key steps were (1) an asymmetric allylation using a chiral allyltitanium reagent and a double-asymmetric Simmons-Smith cyclopropanation to introduce three chiral centers, (2) Wittig and Wittig-Horner reactions to construct the C(3-4) and C(7-10) alkenes, and (3) a direct conversion of the thiazolidine to the thiazoline. Copyright © 1996 Elsevier Science Ltd

Curacin A (**1**) is a novel antimitotic agent isolated from a Caribbean cyanobacterium, *Lyngbya majuscula*,[1] and consists of a disubstituted thiazoline bearing a chiral cyclopropane ring and an aliphatic side chain. It was also reported that curacin A inhibited tubulin assembly by binding to the colchicine-binding site[1], which is one of the two distinct drug-binding sites on tubulin. This result is intriguing because curacin A has little structural similarity to known natural and synthetic colchicine-site ligands. Thus, elucidation of the nature of curacin A-binding to tubulin should afford further insight into the molecular mechanism of tubulin-ligand interaction at this site, and could lead to the development of new bioactive agents.

Several groups have reported synthetic approaches to curacin A.[2-4] The absolute configuration of curacin A was determined by chemical degradation and total synthesis by White *et al.*[2] In our previous paper[3], we reported on the synthesis of 2-(2-methyl)cyclopropyl-4-(1-propenyl)thiazolines as a partial structure of curacin A and also defined the absolute configuration at three chiral centers of the thiazoline-methylcyclopropane moiety in curacin A. In this paper, we describe a highly stereo-controlled total synthesis of curacin A.

The retrosynthetic disconnections are depicted below. We expected that the necessary three double bond geometries could be prepared from geraniol (C(9-10)) by Wittig-Horner reaction (C(7-8)) and Wittig reaction (C(3-4)). The chiral centers at C(2) and C(13) should be derived from a chiral synthon (*L*-cysteine) and an asymmetric allylation using a chiral allyltitanium reagent[5], respectively. The chiral methylcyclopropane moiety could be efficiently prepared from diethyl *L*-tartrate, using a double-asymmetric Simmons-Smith cyclopropanation as a key step. We intended to construct the thiazoline moiety by coupling of the carboxylic acid with the *N*-Boc thiazolidine through selective deprotection of the *N*, *S*-acetal group.

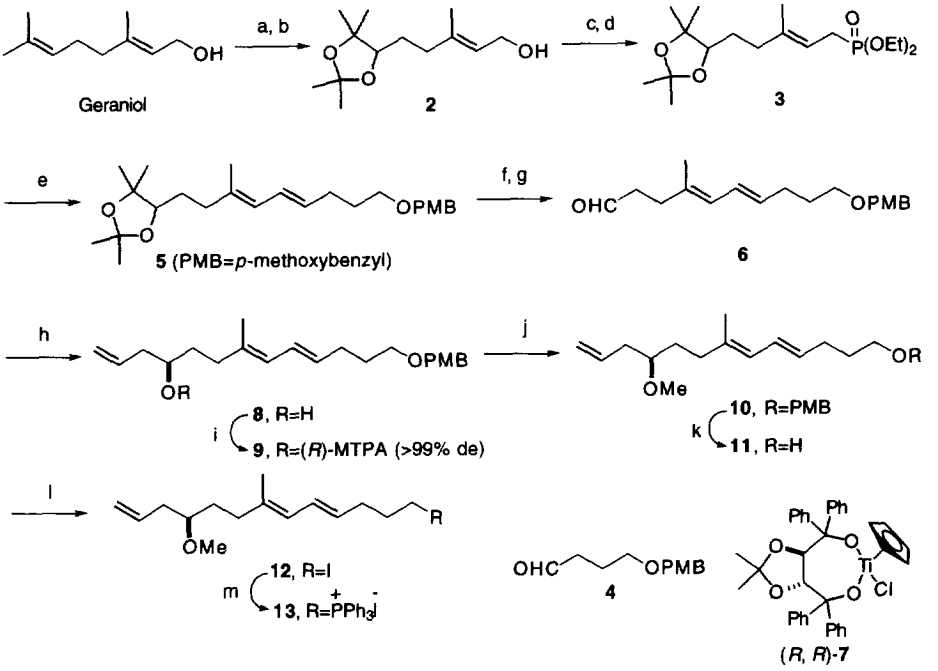


Curacin A (1)

Regioselective epoxidation[6] of geraniol followed by acid-catalyzed hydrolysis and acetalization gave 1, 3-dioxolane **2**, a synthetic equivalent of aldehyde. The compound **2** was converted, *via* the bromide, to the corresponding phosphonate **3** in 75% yield. Wittig-Horner reaction of **3** and the PMB-protected aldehyde **4**, prepared from 1, 4-butanediol, afforded the diene **5** (51%, *E*/*Z*=8.5/1)[7], which was separated by HPLC to give

the desired *E*-isomer. Deacetalization of **5** followed by oxidative cleavage of the diol gave the aldehyde **6** in 93% yield. The asymmetric allylation of **6** with a chiral allyltitanium reagent[5], prepared from [(4*R*, 5*R*)-2, 2-dimethyl-1, 3-dioxolane-4, 5-bis(diphenylmethoxy)]cyclopentadienyl-chlorotitanium ((*R*, *R*)-**7**) and allylmagnesium chloride, proceeded cleanly at -78°C to give the homoallylic alcohol **8** in 95% yield and with excellent enantioselectivity (>99% ee), as determined from the ^{1}H- and ^{13}C-NMR spectra of its Mosher ester **9**. The alcohol **8** was converted to its methyl ether **10** in 89% yield. In deprotection of the PMB group in **10**, treatment with DDQ resulted a complex mixture, but $MgBr_2$·OEt_2-Me_2S treatment proceeded smoothly to give the known and desired alcohol (-)-**11** in 76% yield.[2b, 8] The alcohol **11** was converted, *via* the iodide **12**, to the phosphonium salt **13** according to the reported procedure[2b] (**Scheme 1**).

Scheme 1

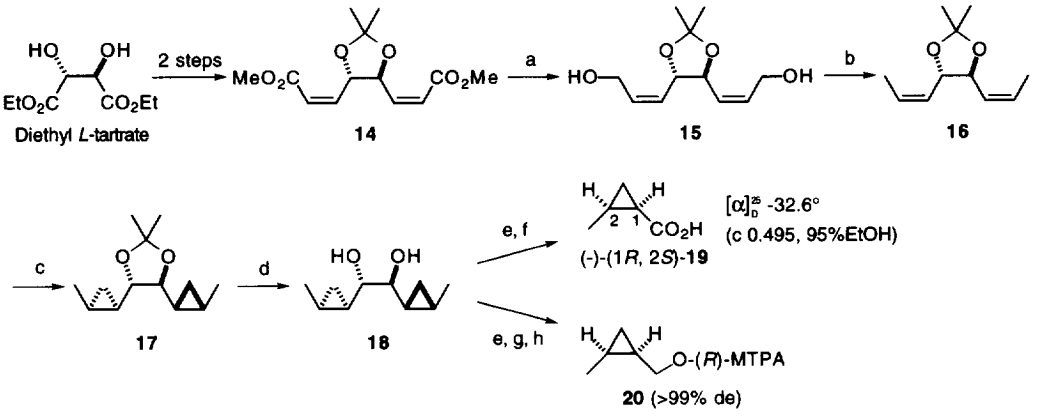


Reagents and conditions: (a) OXONE®, acetone-CH_2Cl_2/phosphate buffer, pH 7.5~8.0, 0°C, 2 h (39% and recovery of geraniol, 37%); (b) PTSA, aq. acetone, 20°C, 2 h (67%); (c) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 1 h; (d) $(EtO)_3P$, benzene, reflux, 2.5 h (75% from **2**); (e) **4**, *t*-BuOK, THF, 20°C, 1.5 h (51%, *E*/*Z*=8.5/1 and recovery of **4**, 13%), then HPLC separation; (f) PTSA, aq. MeOH, 20°C, 5 h (99%); (g) $NaIO_4$, aq. acetone, 20°C, 2 h (94%); (h) allylMgCl, (*R*, *R*)-**7**, THF, 0°C, 1 h, then **6**, THF, -78°C, 1.5 h (95%); (i) (*S*)-(+)-MTPACl, pyridine, CH_2Cl_2, 20°C, 0.5 h (66%); (j) MeI, NaH, DMF, 20°C, 2.5 h (89%); (k) $MgBr_2$·OEt_2, Me_2S, CH_2Cl_2, 20°C, 2 h (76% and recovery of **10**, 6%); (l) MsCl, pyridine, 0°C, 1 h, then NaI, acetone, reflux, 2 h (87%); (m)Ph_3P, MeCN, reflux, 7 h (quant.)

Asymmetric synthesis of the cyclopropane moiety of **1** is shown in **Scheme 2**. We intended to transform two functional groups of diethyl *L*-tartrate simultaneously. The (*Z*, *Z*)-diester **14** was easily prepared from diethyl *L*-tartrate in two steps.[9] Reduction of the diester **14** gave the corresponding bisallyl alcohol **15** in 58% yield. Bromination of **15** followed by reduction with $LiAlH_4$ gave the (*Z*, *Z*)-diene **16** in 69% yield. Double Simmons-Smith reaction of **16** with Et_2Zn-CH_2I_2 or Zn-Cu -CH_2I_2 proceeded with excellent diastereofacial selectivity[10] to give the desired dicyclopropane **17** as the sole product in 63% or 60% yield, respectively. The compound **17** was converted, *via* the diol **18**, to the corresponding aldehyde, which was further oxidized *in situ* with $KMnO_4$[11] to give the known and desired (1*R*, 2*S*)-2-methylcyclopropanecarboxylic

acid **19** in 81% yield. The optical purity (>99% ee) and absolute configuration of **19** were determined from its optical rotation[12] and the ^{1}H- and ^{13}C-NMR spectra of the Mosher ester **20** of the 2-methylcyclopropanemethanol derived from **18**.

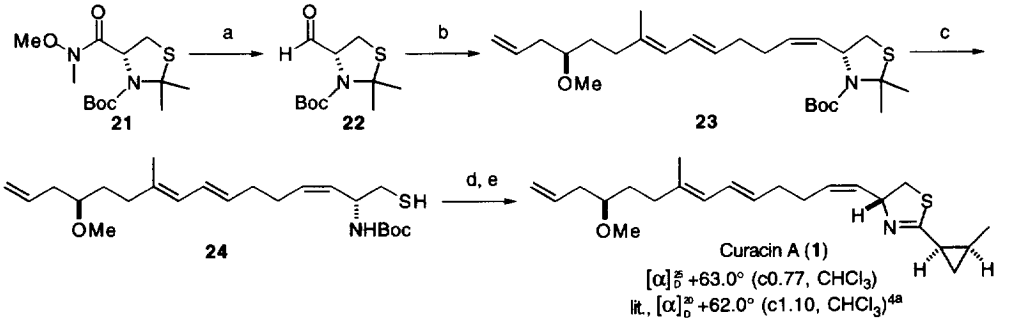
Scheme 2



Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, -78-0°C, 1.5 h (58%); (b) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 0.5 h, then $LiAlH_4$, ether, 35°C, 1 h (69%); (c) Et_2Zn, CH_2I_2, CH_2Cl_2, -25°C, 2.5 h (63%) or Zn-Cu, CH_2I_2, ether, 35°C, 6 h (60%); (d) PTSA, aq. MeOH, 20°C, 2.5 h (92%); (e) $NaIO_4$, CH_2Cl_2-H_2O, 20°C, 1.5 h; (f) $KMnO_4$, *t*-BuOH-aq. KH_2PO_4, 20°C, 2 h (89% from **18**); (g) $NaBH_4$, CH_2Cl_2-MeOH, 0°C, 0.5 h; (h) (*S*)-(+)-MTPACl, pyridine, CH_2Cl_2, 20°C, 1 h (57% from **18**)

The total synthesis of curacin A was accomplished as shown in **Scheme 3**. Reduction of the amide **21** prepared from *L*-cysteine[13] gave the aldehyde **22** in 92% yield. Wittig reaction of the phosphonium salt **13** and the aldehyde **22** afforded the thiazolidine **23** in 60% yield. None of the *E*-isomer was detected by ^{1}H-NMR analysis. The thiazoline moiety of **1** was synthesized from the *N*-Boc thiazolidine **23** in a stepwise manner.[3,14] Selective deprotection of the *N*,*S*-acetal group of **23** was carried out in diluted TFA in water-saturated CH_2Cl_2 to give the *N*-Boc amino thiol **24**, which was converted to the corresponding thiol ester using the carboxylic acid **19** and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl). Deprotection of the *tert*-Boc group of the thiol ester followed by refluxing in benzene, gave curacin A in 10% yield from **23**. The physicochemical properties (^{1}H- and ^{13}C-NMR spectra, optical rotation) of the synthesized curacin A are identical with those reported.[1,4a]

Scheme 3



Reagents and conditions: (a) $LiAlH_4$, ether, 0°C, 0.5 h (92%); (b) **13**, LiHMDS, THF, -78°C, 0.5 h, then **22**, THF, -78-0°C, 2 h (60% and recovery of **22**, 25%); (c) TFA, CH_2Cl_2, 20°C, 6 h; (d) (-)-**19**, BOPCl, Et_3N, CH_2Cl_2, 20°C, 3 h; (e) TFA, CH_2Cl_2, 20°C, 2 h, then benzene, reflux, 2.5 h (10% from **23**)

The effects of the synthesized curacin A and related compounds on microtubule assembly were examined. Curacin A showed high anti-tubulin activity (IC_{50}=2.5 μM) under the conditions used[15], though the PMB ether **10**, the alcohol **11**, the tetraene **25**[16] and the *N*-Boc thiazolidine **23** did not inhibit tubulin polymerization. These and our previous[3] results demonstrate that the combination of heterocyclic and lipid side chain moieties in curacin A is important for its anti-tubulin activity. Studies on the structure-activity relationship of curacin A are in progress.

Acknowledgement

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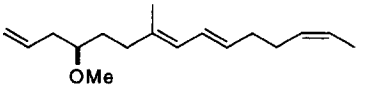

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