

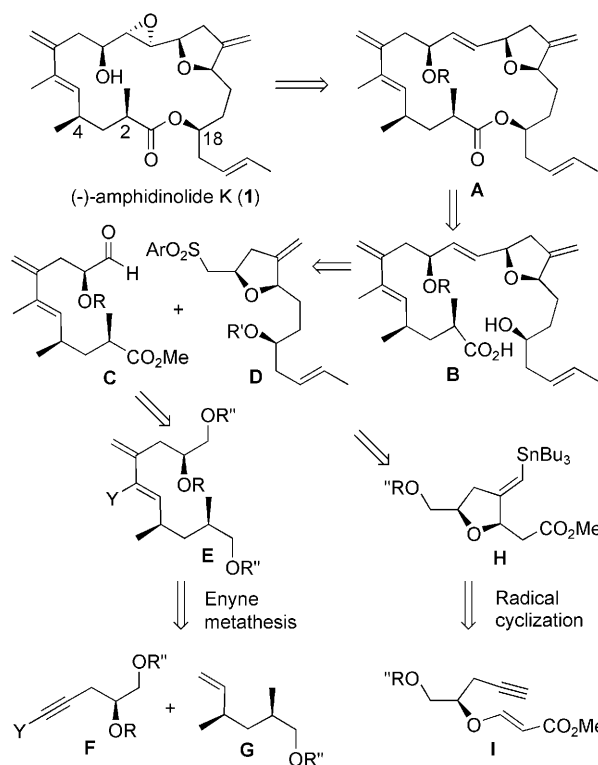
## Total Synthesis of (–)-Amphidinolide K\*\*

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(–)-Amphidinolide K (**1**; see Scheme 1) is a member of the cytotoxic macrolides that were isolated by Kobayashi and co-workers from the laboratory-cultured dinoflagellates *Amphidinium* sp., which are symbionts of the marine flatworms *Amphiscolops* sp. found in Okinawan.<sup>[1]</sup> Amphidinolide K (**1**) is known to possess cytotoxic activity against L1210 ( $IC_{50} = 1.65 \mu\text{g mL}^{-1}$ ) and KB ( $IC_{50} = 2.9 \mu\text{g mL}^{-1}$ ) cancer cells in vitro. The total synthesis of (+)-amphidinolide K reported by Williams and Meyer<sup>[2]</sup> has clarified the problems concerning configurational ambiguities at C2, C4, and C18, and as a result (–)-amphidinolide K (**1**) was found to be the natural product. The unique structural features and potent bioactivity of **1** elicited considerable interest in the synthetic community,<sup>[3]</sup> and herein we wish to report the results of our recent efforts on the synthesis of this intriguing molecule.

In the retrosynthetic analysis, epoxidation of the allylic alcohol intermediate **A** ( $R = H$ ) was envisaged as the final step (Scheme 1). The macrolide intermediate **A** would be obtained by lactonization of the *seco* acid **B**, which would in turn be synthesized through the Julia–Kocienski reaction<sup>[4]</sup> of aldehyde **C** and sulfone **D**. Fragment **C** would be obtained from fragment **E** ( $Y = B(\text{pinacol})$ ) by a Suzuki coupling reaction. Fragment **E** would be the product of the enyne cross-metathesis reaction<sup>[5]</sup> of alkynyl boronate **F** and alkene **G**. In another key step, a radical cyclization reaction<sup>[6]</sup> of the homopropargylic  $\beta$ -alkoxyacrylate **I** would provide the methylenedioxy-substituted oxolane intermediate **H** en route to fragment **D**.

In practice,  $\beta$ -alkoxyacrylate **4** was prepared from the known homopropargylic alcohol **3**<sup>[7]</sup> (Scheme 2). Next, the radical cyclization reaction<sup>[6]</sup> of **4** in the presence of tributylstannane and triethylborane proceeded efficiently and gave mainly (16:1) the *cis*-2,5-disubstituted oxolane intermediate **5** after acidic destannylation. The corresponding aldehyde was converted into the homologous aldehyde **6**, which was then



**Scheme 1.** Retrosynthetic analysis of (–)-amphidinolide K (**1**). Ar = aromatic.

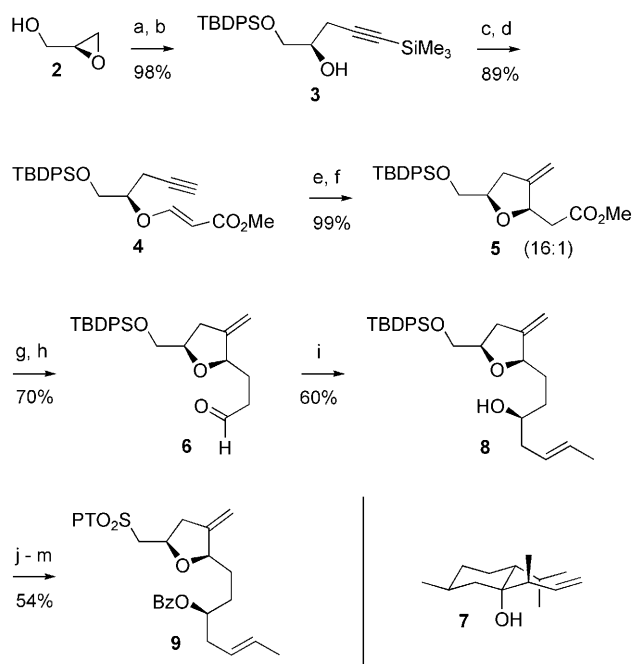
treated with alcohol **7**<sup>[8]</sup> to produce the homoallylic alcohol **8**. After protection of the alcohol as the benzoate derivative, 1-phenyl-1*H*-tetrazolyl sulfone **9** was prepared by using the standard procedures as outlined.

Olefin **12** was prepared from the known alcohol **11**<sup>[9]</sup> through mesylation and subsequent reduction (Scheme 3). Alkyne **14** was prepared from (*R*)-glycidol (**13**) through protection of the alcohol with THP, then treatment with lithium TMS-acetylide, protection with a TBS group, and hydrolytic cleavage of the alkynyl TMS group. Then alkynyl boronate **15** was prepared from alkyne **14** under standard reaction conditions. Subsequently, the enyne cross-metathesis reaction<sup>[5,10]</sup> of **15** with olefin **12** proceeded effectively in the presence of the second-generation Grubbs catalyst to yield a mixture (7.5:1) that favored the desired *E* isomer **16**. The use of alkynyl boronate **15** in the enyne cross-metathesis reaction was important; the use of methyl-substituted alkynes did not yield useful amount of the cross-metathesis products. For the synthesis of diene **17** from vinyl boronate **16**, a Suzuki–

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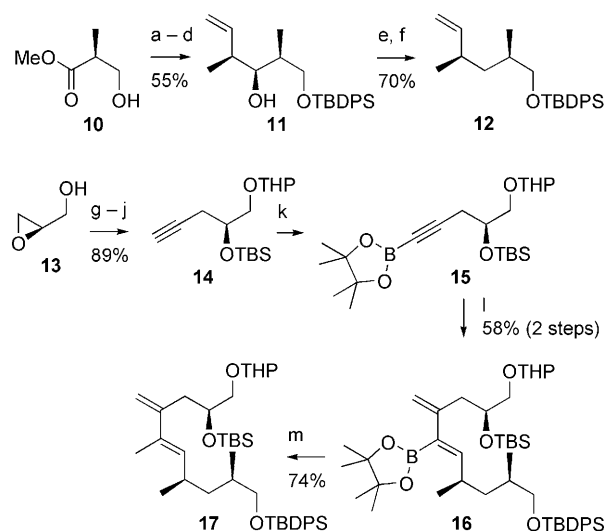


**Scheme 2.** Synthesis of the fragment **D**. a) TBDPSCl; b) LiCCSiMe<sub>3</sub>; c) K<sub>2</sub>CO<sub>3</sub>, MeOH; d) CHCCO<sub>2</sub>Me, NMM, CH<sub>2</sub>Cl<sub>2</sub>; e) *n*Bu<sub>3</sub>SnH, Et<sub>3</sub>B, toluene; f) *p*TsOH, CH<sub>2</sub>Cl<sub>2</sub>; g) DIBAL, CH<sub>2</sub>Cl<sub>2</sub>, −78 °C; h) (Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>OMe)Cl<sup>−</sup>, *t*BuOK, THF; Hg(OAc)<sub>2</sub>, THF/H<sub>2</sub>O (10:1), 0 °C; i) **7**, TFA, CH<sub>2</sub>Cl<sub>2</sub> (0.03 M); j) BzCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; k) TBAF, THF; l) PTSH, DIAD, Ph<sub>3</sub>P, THF; m) (NH<sub>4</sub>)<sub>6</sub>[Mo<sub>7</sub>O<sub>24</sub>]·4 H<sub>2</sub>O, H<sub>2</sub>O<sub>2</sub>, EtOH. Bz = benzoyl, DIAD = diisopropyl azodicarboxylate, DIBAL = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, NMM = *N*-methylmorpholine, PT = 1-phenyl-1*H*-tetrazolyl, TBAF = *t*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

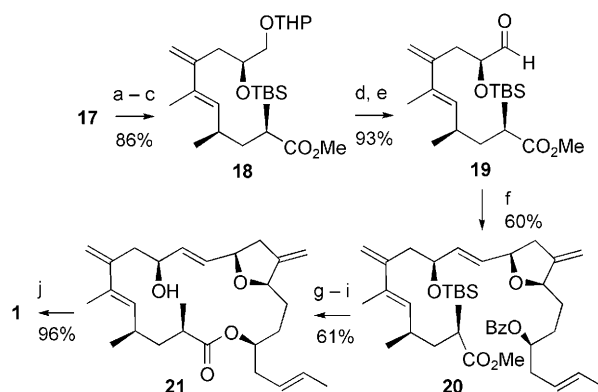
Miyaura reaction was envisioned. Suzuki–Miyaura reaction of **16** using iodomethane did not proceed under the known reaction conditions;<sup>[11]</sup> however, in the presence of thallium ethoxide<sup>[12]</sup> the diene **17** was obtained in 74% yield.

Selective removal of the TBDPS protecting group of **17**, oxidation, and treatment with TMS diazomethane led to the methyl ester **18**, which was further converted into aldehyde **19** by selective removal of the THP protecting group<sup>[13]</sup> and oxidation (Scheme 4). A Julia–Kocienski reaction<sup>[4]</sup> between aldehyde **19** and sulfone **9** in the presence of potassium hexamethyldisilazide proceeded stereoselectively in DMF to yield the *E* olefin **20**. The *seco* acid was obtained from **20** through hydrolysis, and it was converted into the corresponding lactone under modified Yamaguchi reaction conditions.<sup>[14]</sup> Subsequent removal of the TBS protecting group provided the allylic alcohol **21**. (−)-Amphidinolide **K** (**1**)<sup>[15]</sup> was prepared in high yield by asymmetric epoxidation of **21** in the presence of (+)-diethyl tartrate.

The present synthesis represents a highly convergent route to (−)-amphidinolide **K** (**1**) requiring 18 steps in the longest linear sequence (6.8% total yield) from (*S*)-glycidol (**2**). This synthesis presents another successful example of stereoselective radical cyclization reactions of β-alkoxyacrylates.



**Scheme 3.** Synthesis of the fragment **C**. a) TBDPSCl; b) LiBH<sub>4</sub>; c) SO<sub>3</sub>, pyridine, TEA, DMSO; d) (E)-MeCHCHCH<sub>2</sub>B(dIpc)<sub>2</sub>; e) MsCl, TEA/CH<sub>2</sub>Cl<sub>2</sub> (1:2); f) LiAlH<sub>4</sub>, diethyl ether, reflux; g) DHP; h) LiCCSiMe<sub>3</sub>; i) TBSOTf; j) K<sub>2</sub>CO<sub>3</sub>, MeOH; k) *n*BuLi, (pinacol)B(O*i*Pr), THF, −78 °C; HCl, RT; l) **12**, [(H<sub>2</sub>IMes)<sub>2</sub>(P(Cy)<sub>3</sub>)RuCl<sub>2</sub>CHPh] (15 mol %), CH<sub>2</sub>Cl<sub>2</sub>, reflux; m) [Pd(Ph<sub>3</sub>P)<sub>4</sub>] (20 mol %), MeI, TIOEt, THF/H<sub>2</sub>O (3:1). Cy = cyclohexyl, DHP = 3,4-dihydro-2*H*-pyran, DMSO = dimethyl sulfoxide, Ipc = isopinocampheyl, Mes = 2,4,6-trimethylphenyl, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl, TEA = triethylamine, THP = tetrahydropyran.



**Scheme 4.** Synthesis of (−)-amphidinolide **K** (**1**). a) TBAF, THF, 0 °C; b) IBX, DMSO/THF (1:1); NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene/*t*BuOH/H<sub>2</sub>O (1:1:1); c) TMSCHN<sub>2</sub>, MeOH; d) BF<sub>3</sub>·OEt<sub>2</sub>, EtSH/CH<sub>2</sub>Cl<sub>2</sub> (1:5), −30 °C; e) DMP, CH<sub>2</sub>Cl<sub>2</sub>; f) **9**, KHMDS, DMF, −78 °C, 30 min; RT, 1 h; g) NaOH, MeOH/H<sub>2</sub>O (4:1); h) 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>COCl, TEA, DMAP, toluene, reflux; i) TBAF, THF; j) (+)-DET, Ti(O*i*Pr)<sub>4</sub>, TBHP, M.S. (4 Å), CH<sub>2</sub>Cl<sub>2</sub>, −20 °C. DET = diethyl tartrate, DMF = *N,N*-dimethylformamide, DMP = Dess–Martin periodinane, HMDs = 1,1,1,3,3,3-hexamethyldisilazane, IBX = *o*-iodoxybenzoic acid, M.S. = molecular sieves, TBHP = *tert*-butyl hydroperoxide.

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- [15]  $[\alpha]_{\text{D}}^{28} = -75.2 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$  ( $c = 0.0006 \text{ g cm}^{-3}$ , MeOH) ( $[\alpha]_{\text{D}}^{21} = -71 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$  ( $c = 0.0005 \text{ g cm}^{-3}$ , MeOH)<sup>[1a]</sup>). It should be noted that the NMR spectra of (+)-amphidinolide **K** reported by Williams and Meyer<sup>[2]</sup> were actually recorded in  $\text{C}_6\text{D}_6$ , and not in  $\text{CDCl}_3$  as reported.