Natural Product Synthesis

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Total Synthesis of (−)-Amphidinolide K**

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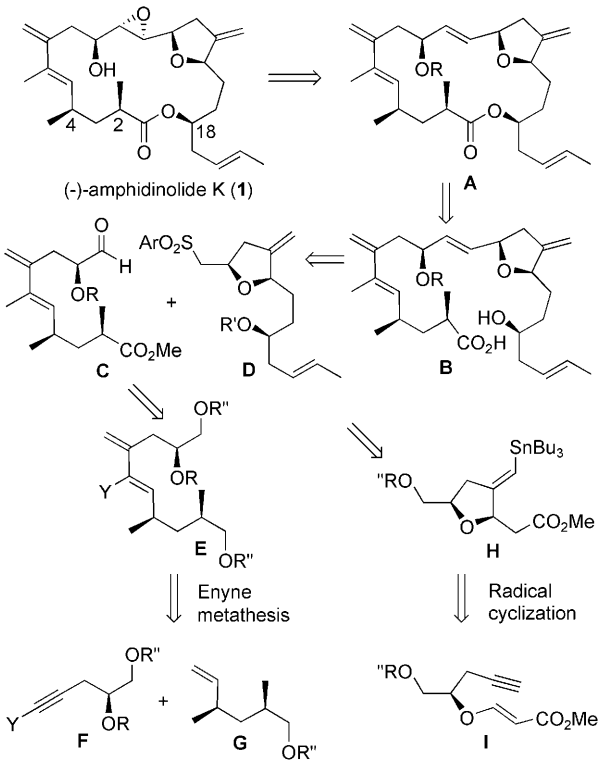
(−)-Amphidinolide K (**1**; see Scheme 1) is a member of the cytotoxic macrolides that were isolated by Kobayashi and coworkers from the laboratory-cultured dinoflagellates *Amphidinium* sp., which are symbionts of the marine flatworms *Amphiscolops* sp. found in Okinawan.[1] Amphidinolide K (**1**) is known to possess cytotoxic activity against L1210 (IC_{50} = 1.65 μg mL^{-1}) and KB (IC_{50} = 2.9 μg mL^{-1}) cancer cells in vitro. The total synthesis of (+)-amphidinolide K reported by Williams and Meyer[2] 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,[3] 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[4] of aldehyde **C** and sulfone **D**. Fragment **C** would be obtained from fragment **E** (Y = B(pinacol)) by a Suzuki coupling reaction. Fragment **E** would be the product of the enyne cross-metathesis reaction[5] of alkynyl boronate **F** and alkene **G**. In another key step, a radical cyclization reaction[6] of the homopropargylic β-alkoxyacrylate **I** would provide the methylidene-substituted oxolane intermediate **H** en route to fragment **D**.



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

In practice, β-alkoxyacrylate **4** was prepared from the known homopropargylic alcohol **3**[7] (Scheme 2). Next, the radical cyclization reaction[6] 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 treated with alcohol **7**[8] 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**[9] 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[5,10] 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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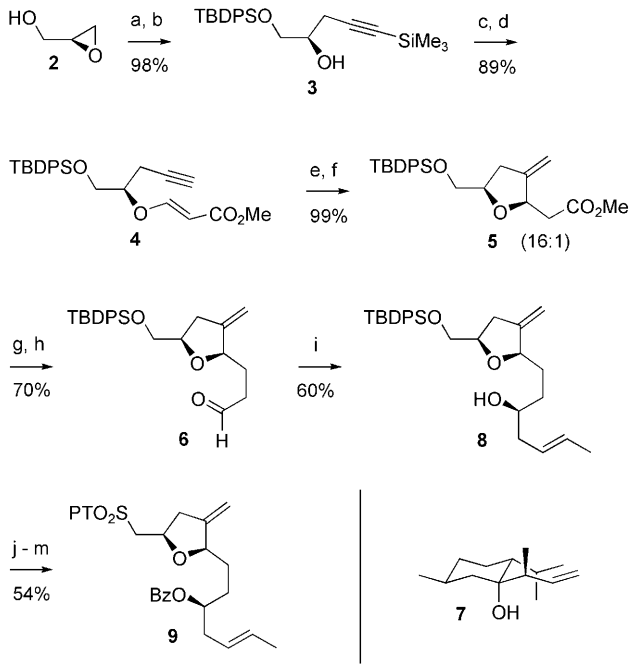
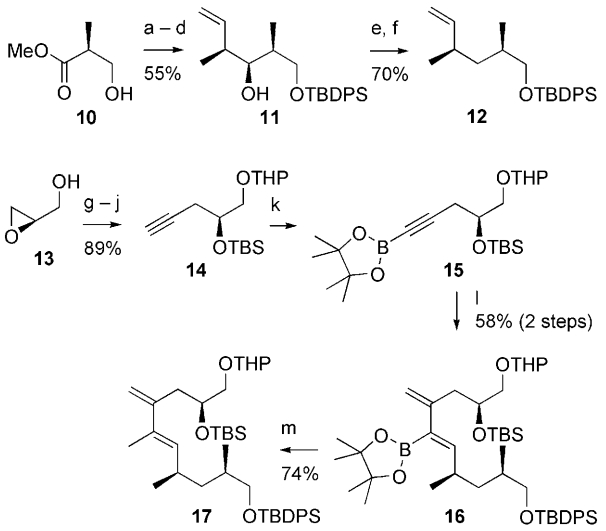
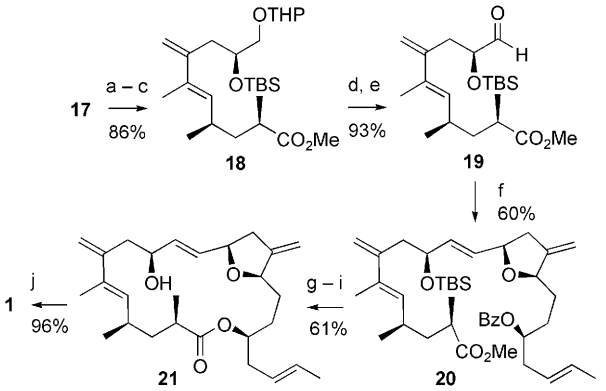


Scheme 2. Synthesis of the fragment **D**. a) TBDPSCl; b) $LiCCSiMe_3$; c) K_2CO_3, MeOH; d) $CHCCO_2Me$, NMM, CH_2Cl_2; e) nBu_3SnH, Et_3B, toluene; f) *p*TsOH, CH_2Cl_2; g) DIBAL, CH_2Cl_2, −78 °C; h) $(Ph_3P^+CH_2OMe)Cl^-$, *t*BuOK, THF; $Hg(OAc)_2$, THF/H_2O (10:1), 0 °C; i) **7**, TFA, CH_2Cl_2 (0.03 M); j) BzCl, DMAP, CH_2Cl_2; k) TBAF, THF; l) PTSH, DIAD, Ph_3P, THF; m) $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$, H_2O_2, EtOH. Bz = benzoyl, DIAD = diisopropyl azodicarboxylate, DIBAL = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, NMM = *N*-methylmorpholine, PT = 1-phenyl-1*H*-tetrazolyl, TBAF = *tetra*-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.



Scheme 3. Synthesis of the fragment **C**. a) TBDPSCl; b) $LiBH_4$; c) SO_3·pyridine, TEA, DMSO; d) (*E*)-$MeCHCHCH_2B(^dIpc)_2$; e) MsCl, TEA/CH_2Cl_2 (1:2); f) $LiAlH_4$, diethyl ether, reflux; g) DHP; h) LiCCSiMe$_3$; i) TBSOTf; j) K_2CO_3, MeOH; k) *n*BuLi, (pinacol)B(*O*i*P*r), THF, −78 °C; HCl, RT; l) **12**, $[(H_2IMes_2)(P(Cy)_3)RuCl_2CHPh]$ (15 mol%), CH_2Cl_2, reflux; m) $[Pd(Ph_3P)_4]$ (20 mol%), MeI, TlOEt, THF/H_2O (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 = tetrahydropyranyl.



Scheme 4. Synthesis of (−)-amphidinolide K (**1**). a) TBAF, THF, 0 °C; b) IBX, DMSO/THF (1:1); $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*t*BuOH/H_2O (1:1:1); c) $TMSCHN_2$, MeOH; d) $BF_3\cdot OEt_2$, EtSH/CH_2Cl_2 (1:5), −30 °C; e) DMP, CH_2Cl_2; f) **9**, KHMDS, DMF, −78 °C, 30 min; RT, 1 h; g) NaOH, MeOH/H_2O (4:1); h) 2,4,6-$Cl_3C_6H_2COCl$, TEA, DMAP, toluene, reflux; i) TBAF, THF; j) (+)-DET, $Ti(OiPr)_4$, TBHP, M.S. (4 Å), CH_2Cl_2, −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.

Miyaura reaction was envisioned. Suzuki–Miyaura reaction of **16** using iodomethane did not proceed under the known reaction conditions;[11] however, in the presence of thallium ethoxide[12] 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[13] and oxidation (Scheme 4). A Julia–Kocienski reaction[4] 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.[14] Subsequent removal of the TBS protecting group provided the allylic alcohol **21**. (−)-Amphidinolide K (**1**)[15] 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.

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[15] $[\alpha]_D^{28} = -75.2\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.0006\ \mathrm{g\,cm^{-3}}$, MeOH) ($[\alpha]_D^{21} = -71\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.0005\ \mathrm{g\,cm^{-3}}$, MeOH)[1a]). It should be noted that the NMR spectra of (+)-amphidinolide K reported by Williams and Meyer[2] were actually recorded in C_6D_6, and not in $CDCl_3$ as reported.

