Communications

Studies on the Total Synthesis of Amphidinolide O (III): A Stereoselective Synthesis of C1-C11 Fragment

Jong Woo Kim, Sun-Ju Kong, Yeo-Jin Kim, and Duck-Hyung Lee*

*Department of Chemistry, Sogang University, Seoul 121-742, Korea. *E-mail: dhlee@sogang.ac.kr*

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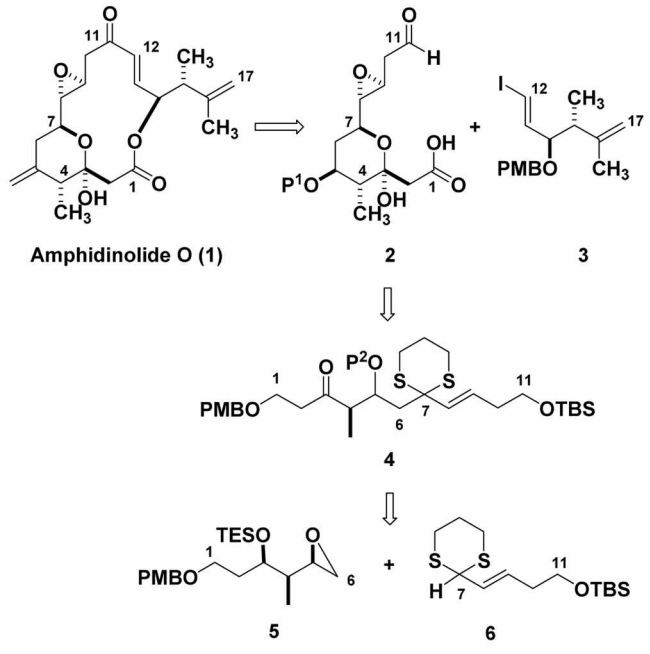
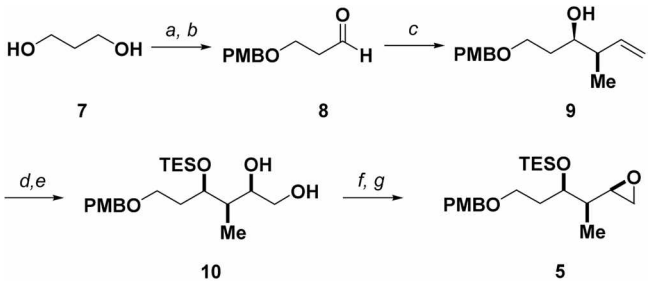
The amphidinolides are well-known series of cytotoxic macrolides isolated from the marine dinoflagellate *Amphidinium* sp., a symbiotic with Okinawan marine flatworm *Amphiscolops* sp. These series of compounds attracted much interest of the synthetic chemists around the world. In fact, total synthesis of amphidinolide A, E, H, G, J, K, P, T, W, X, and Y were reported,[1] and many synthetic studies for amphidinolide B, C, F, and L, have been published.[2]

In relation to our program for the synthesis of amphidinolide O (**1**), which exhibited *in vitro* cytotoxicity against L1210 (IC_{50} 1.7 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} 3.6 μg/mL),[3] we reported the synthesis of C12-C17,[4a] C3-C11,[4b] and C1-C11[4c] fragments of amphidinolide O (**1**) for the past few years. We report herein a new synthetic route to C1-C11 fragment **4** of amphidinolide O (**1**) *via* a ring-opening reaction of epoxide **5** by dithiane **6** as a key step.

In a retrosynthetic point of view (Scheme 1), the amphidinolide O (**1**) can be dissected into two fragments, the C1-C11 fragment **2** bearing the epoxide and the hemiketal moieties and the C12-C17 vinyl iodide fragment **3**.[4a] The hemiketal **2** would be derived from the acyclic precursor **4**, and the precursor **4** could be cleaved into the epoxide **5** and dithiane **6**. The intermediate **5** and **6** would be prepared from a common starting material, 1,3-propanediol (**7**).



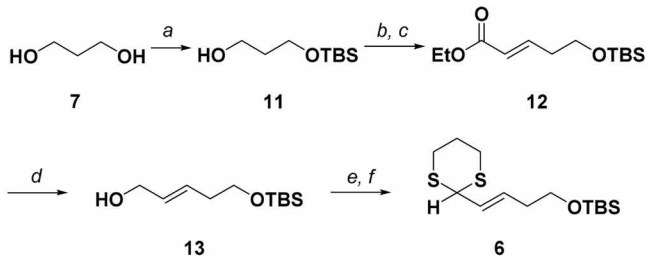
Scheme 1. Retrosynthesis of amphidinolide O (1).



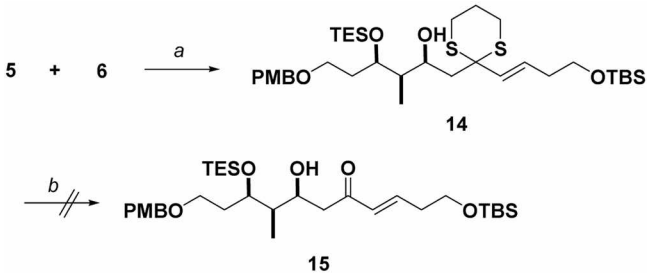
Scheme 2. Synthesis of C1-C6 epoxide fragment **5**. (a) NaH, PMBCl, THF, 70 °C, 5 day, 84%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 99%; (c) *t*-BuOK, *cis*-2-butene, *n*-BuLi, THF, −78 °C, 5 min, then −45 °C, 20 min; (−)-Ipc_2BOMe, −78 °C, 40 min, then BF_3OEt_2, **8**, −78 °C, 3 hr; 3 N NaOH, 30% H_2O_2, 72%; (d) TESCl, DMAP, pyr., rt, 6 hr, 99%; (e) AD-mix β, *t*-BuOH, H_2O, rt, 12 hr, 83%; (f) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, 6 hr, 88%; (g) DBU, CH_2Cl_2, rt, 90 min, 72%.

The synthesis of the C1-C6 epoxide was summarized in Scheme 2. Monoprotection of the diol **7** as a PMB ether using sodium hydride and PMBCl in THF was followed by Swern oxidation to afford the aldehyde **8** in 83% two-step yield. Diastereoselective crotylation of aldehyde **8** by *in-situ* generated (*Z*)-(−)-Ipc_2B-crotyl reagent proceeded efficiently to produce the alcohol **9** in 72% yield.[5] Protection of the hydroxy group of **9** by treatment of TESCl and DMAP in 99% yield and Sharpless asymmetric dihydroxylation of the terminal double bond in 83% yield[6] provided the diol **10**. Finally, the 1,2-diol **10** was transformed into the epoxide **5** *via* a two-step sequence, tosylation of primary alcohol with tosyl chloride and DMAP in TEA/CH_2Cl_2 (1:1) and subsequent cyclization with DBU in CH_2Cl_2,[7] in 63% overall yield.

The C7-C11 fragment **6** was prepared as shown in Scheme 3. 1,3-Propanediol (**7**) was treated with *t*-butyldimethylsilyl



Scheme 3. Synthesis of C7-C11 dithiane fragment **6**. (a) TBSCl, imidazole, CH_2Cl_2, rt, 3 day, 72%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 99%; (c) $Ph_3P{=}CHCO_2Et$, toluene, 45 °C, 1 hr, 89%; (d) DIBAL, CH_2Cl_2, −78 °C, 1 hr, 91%; (e) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 99%; (f) 1,3-propanedithiol, $Mg(ClO_4)_2$, ether, rt, 12 hr, 62%.



Scheme 4. Coupling of intermediate **5** and **6**. (a) (i) **6**, *n*-BuLi, THF, −78 °C, 20 min; −20 °C, 40 min (ii) **5**, −78 °C; −20 °C, 1 hr, 62%. (b) Reaction conditions (see the text for details).

chloride and imidazole to afford the primary alcohol **11** in 72% yield. Swern oxidation of **11** and subsequent Wittig reaction produced *trans*-α,β-unsaturated ester **12** in 88% overall yield. And the ester **12** was converted to allylic alcohol **13** by reduction with DIBAL at −78 °C in 91% yield. The alcohol **13** was then oxidized quantitatively using Swern protocol and the resulting aldehyde was protected immediately with 1,3-propanedithiol using $Mg(ClO_4)_2$ in ether to complete the synthesis of **6** in 62% yield.[8]

With key intermediates **5** and **6** in our hands, coupling of **5** and **6** for the synthesis of acyclic precursor **14** was carried out immediately by *n*-BuLi in THF in 62% yield (Scheme 4).[9] However, final elaboration to deprotect the 1,3-dithiane moiety using standard reaction conditions such as MeI, NCS, NBS, $Hg(ClO_4)_2$, or $AgNO_3$ failed to provide the desired ketone **15**. Starting material **14** was recovered or decomposed[10] in every case and further investigations on this issue will be in progress.

In summary, starting from 1,3-propanediol (**7**), we have prepared epoxide **5** *via* 7-step sequence in 31% overall yield and dithiane **6** *via* 6-step sequence in 35% overall yield. Although the coupling of **5** and **6** was achieved easily in 62% yield, deprotection of the dithiane moiety was not successful so far.

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