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Communications

Toward the Total Synthesis of Amphidinolide O: An Enantioselective Synthesis of C3-C8 Fragment

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Amphidinolide O (**1**) was isolated from the laboratory cultured Okinawan marine dinoflagelate *amphidinolium* sp. by Kobayashi *et al.*,[1] and shows *in vitro* cytotoxicity against murine lymphoma L1210 (IC_{50} = 1.7 mg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 1.6 mg/mL). Amphidinolide O (**1**) is a medium-sized macrolide with unusual structural features such as seven chiral centers, C5 exo-methylene double bond and six-membered ring bridge with hemiacetal moiety.[2] We already published several papers concerning the synthesis of amphidinolide O (**1**), and total synthesis of **1** was not reported yet by any other group.[3] We describe herein the enantioselective synthesis of C3-C8 fragment of amphidinolide O (**1**).

Retrosynthetic analysis was described in Figure 1. Amphidinolide O (**1**) might be assembled from two intermediates **2** and **3** *via* esterification and ring closing metathesis as key steps. Intermediate **4**, a precursor to **3** as well as the target molecule in this paper, involves the γ,δ-unsaturated ester moiety along with α,β-chiral substituents with *anti*-stereochemical relationship. Those structural features could be available by Ireland-Claisen rearrangement of the corresponding (*E*)-enolate derived from the propionate ester **5**. The ester **5** was prepared from the commercially available L-(−)-malic acid.

The synthesis of the allyl alcohol **10** was summarized in Scheme 1. Two carboxylic acid moieties of L-malic acid was reduced easily by borane-dimethyl sulfide complex to produce 1,2,4-butanetriol **6**, and selective protection of 1,3-diol moiety over the 1,2-diol moiety was performed successfully by reaction with benzaldehyde dimethyl acetal and PPTS in 82% two-step yield.[4] After the primary alcohol **7** was oxidized using Swern protocol,[5] the resulting aldehyde **8** was subjected to Horner-Wadsworth-Emmons olefination reaction to provide the conjugated ester **9** in 67% two-step yield.[6] The ethyl ester **9** was then reduced by DIBAL-H at −78 °C to give the primary allyl alcohol **10** in 82% yield.

Synthesis of ester **4** was completed *via* 6-step sequence from allyl alcohol **10** (Scheme 2). The primary alcohol **10** was treated with *p*-methoxybenzyl chloride and sodium hydride to afford the PMB ether **11** in 98% yield. The acetal moiety of **11** was removed quantitatively by CSA in aqueous methanol and the primary hydroxyl group of the resulting

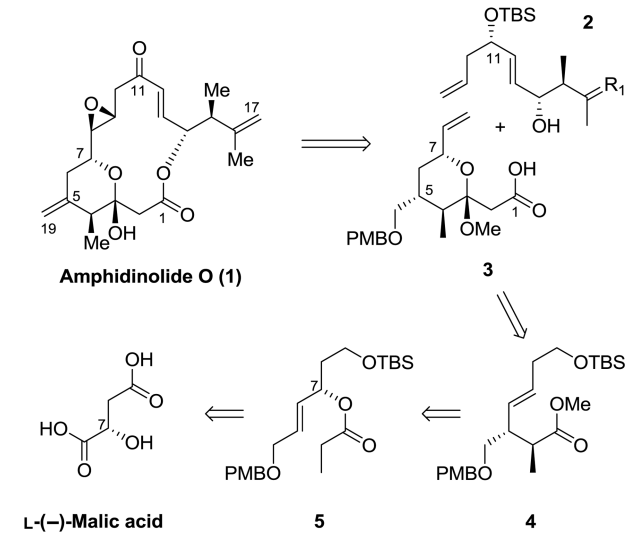
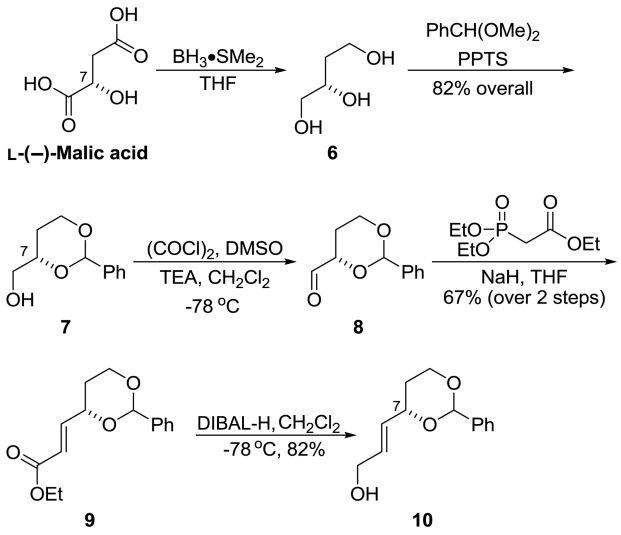
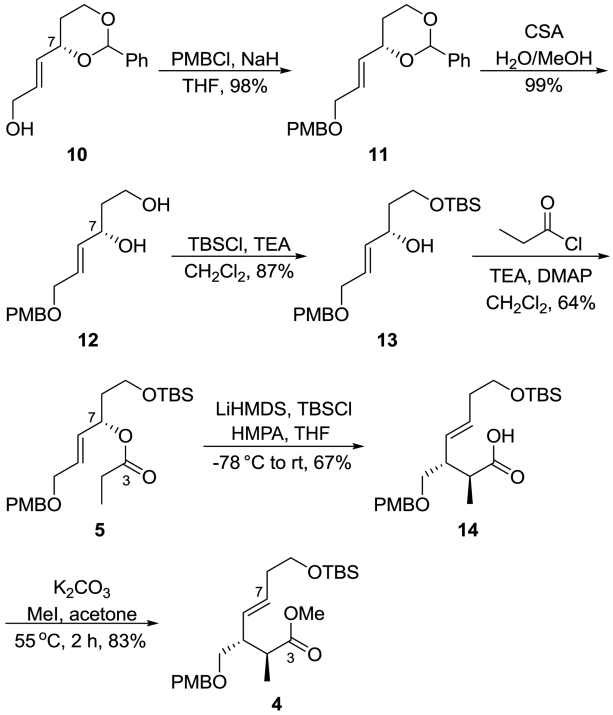


Figure 1. Retrosynthetic analysis.



Scheme 1. Synthesis of allyl alcohol **10**.



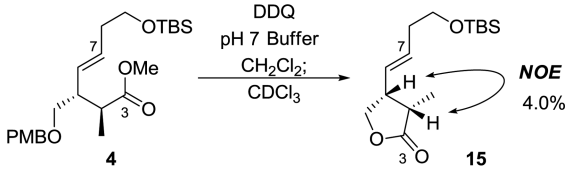
Scheme 2. Synthesis of methyl ester **4**.

diol **12** was protected selectively using TBSCl-TEA combination to provide the secondary alcohol **13** in 87% yield. The intermediate **5**, a key precursor for the Ireland-Claisen rearrangement,[7] was prepared by reaction of **13** with propionyl chloride, TEA, and DMAP in 64% yield.

Two chiral centers in **14** were installed from the C7 chiral center in **5** *via* Ireland-Claisen rearrangement. In other words, intermediate **5** was treated with LiHMDS and TBSCl in THF at −78 °C to give the (*E*)-enolate selectively, which undergoes Claisen rearrangement stereoselectively at room temperature to afford the carboxylic acid **14** with the correct relative stereochemistries in 67% yield.[7] Finally, the methyl ester **4** was prepared by methylation of the corresponding carboxylate with iodomethane and potassium carbonate in 83% yield.[8]

The relative configuration of the methyl ester **4** was confirmed as follows. Treatment of **4** with DDQ in a biphasic mixture of pH 7 buffer solution and CH_2Cl_2 allowed the deprotection of the PMB protecting group and spontaneous cyclization to the lactone **15**. The ^{1}H-NOE experiment clearly showed the relative stereochemistry of **15**, and therefore the methyl ester **4** as drawn in Scheme 2 and 3.

In summary, the methyl ester **4**, a C3-C8 fragment of amphidinolide O (**1**), was prepared enantioselectively *via* 11 steps in 14% overall yields. The diastereoselective Ireland-



Scheme 3. Synthesis of lactone **15**.

Claisen rearrangement of **5** *via* the corresponding (*E*)-enolate intermediate was used as a key step in order to implement the C4 and C5 chiral centers.

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8. Spectroscopic data of methyl ester **4**. R_f 0.57 (1:4 = EtOAc/ Hexane); IR (neat, cm^{-1}): 2953, 2857, 2254, 1734, 1639, 1612, 1587, 1514, 1463, 1361, 1302, 1249, 1204, 1173, 1096, 1038, 971, 835, 776; $[\alpha]_D^{25}$ = 40.5 (*c* 0.35, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.55-5.38 (m, 2H), 4.40 (br, s, 2H), 3.80 (s, 3H), 3.589 (t, *J* = 6.8 Hz, 2H), 3.588 (s, 3H), 2.72-2.66 (m, 1H), 2.58-2.52 (m, 1H), 2.22 (q, *J* = 6.4 Hz, 2H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (CDCl3, 100 MHz) δ 176.0, 131.6, 129.9, 129.1, 128.8, 114.1, 113.4, 72.9, 70.9, 63.3, 55.5, 55.3, 41.2, 40.3, 36.5, 26.1, 18.5, −4.5, −5.0; HRMS (*m/z*) calcd for $C_{24}H_{40}NaO_5Si$ $[M+Na]^+$ 459.2543, found 459.2543.