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Convergent and Enantioselective Total Synthesis of (−)-Amphidinolide O and (−)-Amphidinolide P

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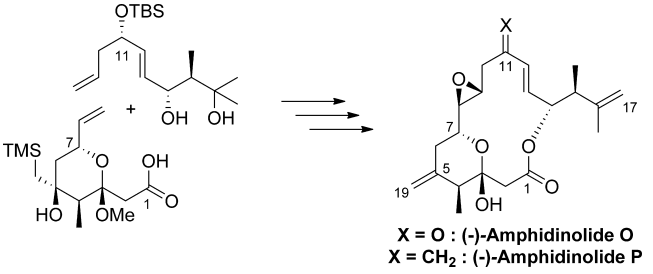
ABSTRACT



A convergent and enantioselective total synthesis of (−)-amphidinolide O (1) and P (2), 15-membered macrolides with seven chiral centers along with many functional groups, is described. The key reactions include enantioselective Brown allylation, *anti*- and *syn*-selective aldol reactions, (*E*)-selective olefin metathesis, conformation-controlled stereoselective epoxidation, and selective introduction of the exomethylene group. Assignments of the absolute stereochemistries of the natural (+)-amphidinolide O (*ent*-1) and P (*ent*-2) are also discussed in detail.

Amphidinolides A−H and J−Y, isolated from laboratory-cultured Okinawan marine dinoflagelate *amphidinolium* sp. by Kobayashi and co-workers, have attracted much attention from the synthetic community because of their biogenetically unusual structural features and cytotoxic activities against various cancer cell lines.[1] Among them, (+)-amphidinolide O (***ent*-1**) and (+)-amphidinolide P (***ent*-2**) have shown in vitro cytotoxicity against murine lymphoma L1210 (IC50 = 1.7 and 3.6 μg/mL, respectively) and human epidermoid carcinoma KB cells (IC50 = 1.6 and 5.8 μg/mL, respectively).[2]

Amphidinolide O (**1**) and P (**2**) have many structural features in common such as a novel 15-membered macrolide with an epoxide at C8−C9, one double bond at C12−C13, one exocyclic double bond at C5, and one 6-membered ring bridged hemiacetal moiety. They have a different functional group only at the C11 position. In other words, amphidinolide O (**1**) has a C11 carbonyl group whereas amphidinolide P (**2**) has a C11 exomethylene group (Scheme 1).[2] So far, two total syntheses and one formal synthesis of amphidinolide P have been reported by three groups.[3] However, their synthetic schemes do not allow the transformation of amphidinolide P into amphidinolide O because the C11 exocyclic double bond moiety was installed at an early stage of the synthesis. We have already published five preliminary papers in relation to the convergent enantioselective total synthesis of (+)-amphidinolide O (***ent*-1**) and P (***ent*-2**),[4] and we report herein the

(1) (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753–1769. (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131–149. (c) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93. (d) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451–460. (e) Morris, J. C.; Phillips, A. J. *Nat. Prod. Rep.* **2009**, *26*, 245–65. (f) Fuerstner, A. *Isr. J. Chem.* **2011**, *51*, 329–345.

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first convergent and enantioselective total synthesis of (−)-amphidinolide O (**1**) and (−)-amphidinolide P (**2**) as well as the confirmation of the absolute stereochemistry of the natural products.

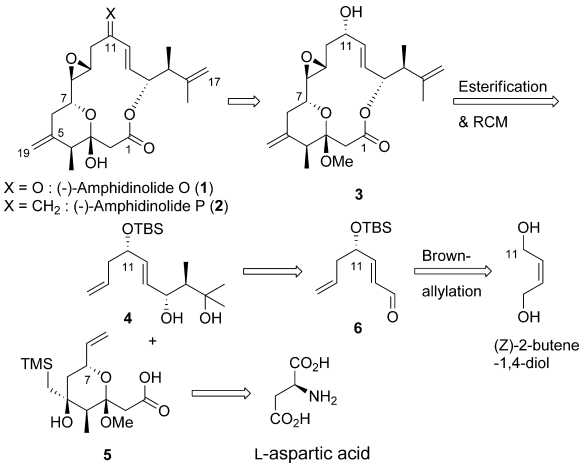
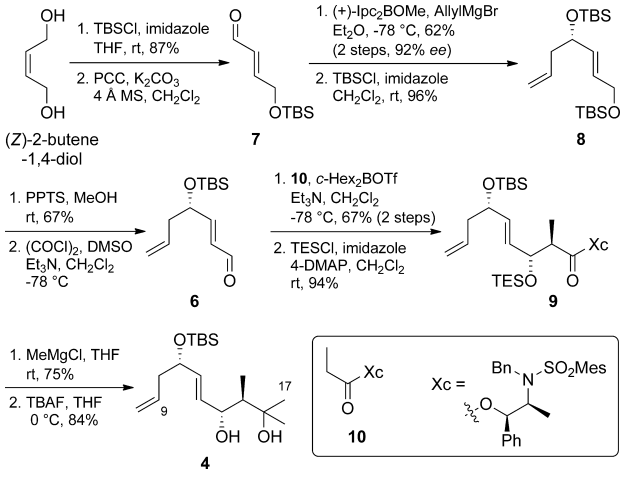


Figure 1. Retrosynthetic analysis of (−)-amphidinolide O (**1**) and (−)-amphidinolide P (**2**).

The retrosynthetic analysis for compounds **1** and **2** is depicted in Figure 1. From their structural similarity, we envisaged that **1** and **2** might be constructed from the common intermediate **3**. The intermediate **3** could be available from the esterification reaction between the diol **4** and the carboxylic acid **5** followed by the ring-closing metathesis (RCM). In order to perform the regioselective epoxidation at the C8−C9 double bond, two *exo*-methylene groups at C5−C19 and C16−C17 should be installed after the C8−C9 epoxide formation. Intermediate **4** could be prepared from *anti*-aldol reaction of **6**,[5] which in turn might be obtained from (*Z*)-2-butene-1,4-diol *via* oxidation and Brown asymmetric allylation.[6] Carboxylic acid **5** could be accessible from L-aspartic acid *via* Evans *syn*-aldol reaction[7] and acid catalyzed cyclization as key steps.

The synthesis of C9−C17 fragment **4** is summarized in Scheme 1. Monosilylation of (*Z*)-2-buten-1,4-diol with TBSCl (87% yield) and PCC oxidation of the remaining primary alcohol resulted in concomitant isomerization of the (*Z*)-conjugated aldehyde into the thermodynamically more stable (*E*)-isomer **7**.[8] Brown asymmetric allylation of aldehyde **7** was carried out to afford the (11*S*)-selective secondary alcohol in a 62% two-step yield with 92% *ee*.[6] Protection of the secondary hydroxyl group with TBSCl provided compound **8** (96% yield). Selective deprotection of the primary TBS group using PPTS in methanol (67% yield) followed by Swern oxidation of the resulting primary alcohol produced the (*E*)-conjugated aldehyde **6**. *Anti*-selective aldol reaction between aldehyde **6** and Masamune's norephedrine-derived auxiliary **10** yielded a secondary alcohol (67% yield over two steps),[5] which was subsequently protected by TESCl to give an ester **9** in 94% yield. Treatment of the ester **9** with MeMgBr in THF (75% yield) and deprotection of the secondary TES protecting group by TBAF (84% yield) produced the C9−C17 fragment **4**.

Scheme 1. Synthesis of C_9−C_{17} Fragment **4**



Synthesis of the C1−C8 fragment **5** is summarized in Scheme 2. L-Aspartic acid was treated with KBr−$NaNO_2$−H_2SO_4 reagent to convert the amino group into the corresponding bromide with retention of configuration *via* a diazonium salt-mediated double inversion strategy. Subsequently, two carboxylic acids were reduced with borane to provide a diol in a 79% two-step yield. The diol was then subjected to NaH-promoted epoxidation and in situ protection of remaining alkoxide with TBSCl to afford the epoxide **11** (74% yield).[9] The epoxide ring of **11** was treated with the lithium ylide derived from trimethylsulfonium iodide and LHMDS to give the allyl secondary alcohol in 88% yield,[10] and the resulting secondary alcohol was converted to the aldehyde **12** via a three-step sequence: (a) TBS protection of the secondary alcohol (100% yield), (b) selective deprotection of the primary TBS group (82%), and (c) Swern oxidation of the primary alcohol (90% yield).

A *syn*-selective aldol reaction of aldehyde **12** using Evans chiral oxazolidinone **18** in the presence of (−)-sparteine afforded the aldol product **13** (83% yield).[7] The chiral auxiliary in compound **13** was converted to the Weinreb

(5) (a) Abiko, A.; Liu, J.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587. (b) Abiko, A. *Org. Synth.* **2003**, *79*, 109–115.

(6) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093.

(7) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77–82. (c) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83–91.

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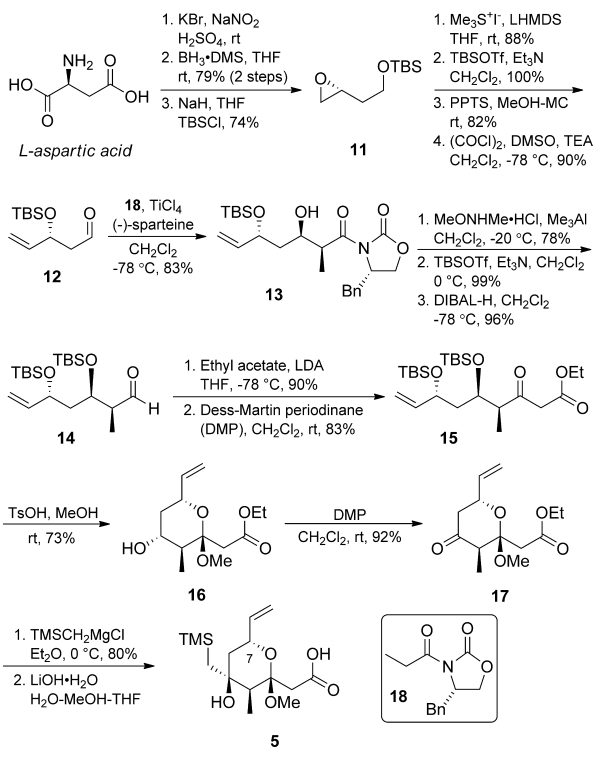
(10) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449–5452.

Scheme 2. Synthesis of C_1-C_8 Fragment



amide (78% yield),[11] the secondary hydroxyl group was protected by TBS group (99% yield), and the Weinreb amide was treated by DIBAL-H to provide the aldehyde **14** (96% yield). Reaction of the lithium enolate derived from ethyl acetate with the aldehyde **14** proceeded smoothly to afford the β-hydroxy ester in 90% yield, and the secondary hydroxyl group was oxidized by Dess-Martin periodinane to provide the β-keto ester **15** in 83% yield. Exposure of **15** with TsOH in MeOH resulted in the deprotection of two TBS protecting groups followed by concomitant cyclization and acetalyzation to afford the cyclic acetal **16** in 73% yield. After the oxidation of the C5 hydroxyl of **16** with Dess-Martin periodinane (92% yield), 1,2-addition of $TMSCH_2MgCl$ to the ketone **17** was carried out successfully to afford the β-hydroxysilane **19** in 80% yield. Finally, the ethyl ester group was removed under basic conditions to afford the crude C1−C8 fragment **5**, which was used in the next step without further purification.

The stereochemical configuration at the C5 chiral center can be explained by steric effects. In other words, the nucleophile approaches from the least hindered face of the ketone **17** (*anti* to both the equatorial C4-methyl group and axial C3-methoxy group), and this relationship was supported strongly by the 2D-NOE experiment of the intermediate **19** (Figure 2).[12]

(11) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4172. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.

(12) 2D-NOE data for **19** are available in the Supporting Information (SI).

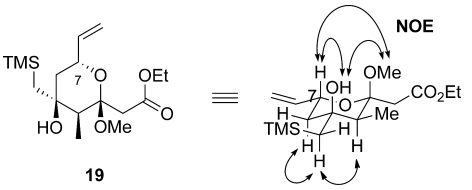


Figure 2. Assignment of the relative stereochemistry of β-hydroxylsilane **19**.

With key intermediates **4** and **5** in hand, we proceeded with the synthesis of (−)-amphidinolide O (**1**) and (−)-amphidinolide P (**2**) (Scheme 3). Intermediates **4** and **5** were coupled using the EDCI-DMAP protocol to afford the ester in 94% yield, and the ester was subjected to olefin metathesis to implement the (*E*)-selective C8−C9 double bond in 93% yield.[13] Formation of the (*E*)-double bond was deduced by measuring the coupling constant (J = 16 Hz) between C8−H and C9−H. Although the epoxidation reaction of **20** by *m*-CPBA proceeded smoothly only at the C8−C9 double bond to give the epoxide **21** in 88% yield, the relative stereochemistry at the C8−C9 epoxide was unclear at this point because the facial selectivity in the epoxidation reaction could not be confirmed completely from its 1D and 2D ^{1}H NMR spectra.[14]

Dehydration of **21** with Martin sulfurane introduced the C16−C17 double bonds (71% yield).[15] Peterson olefination of the β-hydroxysilane moiety was carried out successfully with PCC (64% yield),[16] and deprotection of the C11-OTBS group with TBAF produced the intermediate **3** (86% yield). Oxidation of the C11 hydroxyl group in **3** with Dess-Martin periodinane furnished the ketone **22**, a common key intermediate for the convergent synthesis of **1** and **2**.

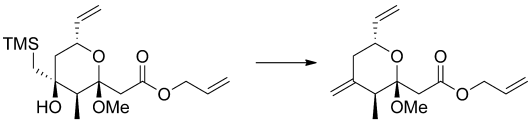
(−)-Amphidinolide O (**1**) was obtained in a 93% two-step yield from **3** by subjection of the ketone **22** to the acidic acetal hydrolysis conditions. The ^{1}H and ^{13}C spectroscopic data and HRMS data of **1** were identical in all respects with the reported data for the natural (+)-amphidinolide O (***ent*-1**). The issue of absolute stereochemistry will be discussed soon.

(13) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(14) Prediction of the stereochemistry in the epoxidation reaction is described in the SI.

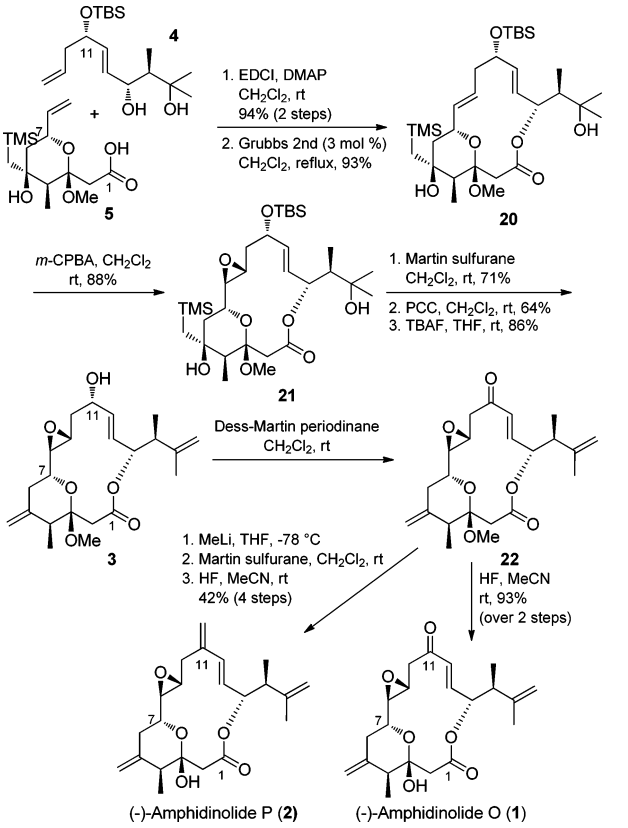
(15) (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329. (b) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010.

(16) (a) Wang, Z.; Jimenez, L. S. *Tetrahedron Lett.* **1996**, *37*, 6049–6052. (b) Several reaction conditions for the Peterson olefination were investigated using the intermediate **X** as a reference material. The starting material **X** remained intact with silica gel and decomposed by treatment of KH, NaH, or *t*-BuOK. Fortunately, HF-pyridine and PCC provided the desired product in 71% and 69% yield, respectively.



X

Scheme 3. RCM and Completion of Amphidinolide O (**1**) and P (**2**)



Next, several approaches for (−)-amphidinolide P (**2**) were investigated starting from the common intermediate **22**, and the best route was determined to be very simple and straightforward. The addition of methyl lithium to the ketone moiety of **22**, direct dehydration with Martin sulfurane as above,[17] and deprotection of the acetal group by HF in H_2O−CH_3CN provided the compound **2** in a 42% four-step yield. Again, the ^1H and ^{13}C spectroscopic data and HRMS data of **2** were identical in all respects with those of the natural (+)-amphidinolide P (***ent*-2**).

Now, we need to clarify the issue of absolute stereochemistry for the natural (+)-amphidinolide O (***ent*-1**) and (+)-amphidinolide P (***ent*-2**). In 2000, the Williams group reported the first enantioselective total synthesis of amphidinolide P (***ent*-2**) along with the optical rotation ($[\alpha]^{20}_D$ −30° (*c* 0.09, MeOH)).[3a] However, an inconsistency in the absolute stereochemistry was found unexpectedly when the Trost group published the synthesis of amphidinolide P (**2**) and its optical rotation ($[\alpha]^{20}_D$ −27.4° (*c* 0.17, MeOH)) in 2004.[3b] Recently, the synthesis and structural correction for amphidinolide P was detailed in a full paper by the Williams group.[3e,f] The optical rotation of $[\alpha]^{20}_D$ −29.2° (*c* 0.31, MeOH) for our synthetic compound **2** is in accord with the Trost result and the recently revised assignment by Williams, confirming clearly that the natural (+)-amphidinolide P is ***ent*-2** ($[\alpha]^{20}_D$ +31° (*c* 0.098, MeOH)).[2]

The optical rotation of our synthetic compound **1** was measured to be $[\alpha]^{23}_D$ −129° (*c* 0.13, MeOH), $[\alpha]^{23}_D$ −131° (*c* 0.20, MeOH), and $[\alpha]^{23}_D$ −137° (*c* 0.25, MeOH). In comparison with the literature value for the natural (+)-amphidinolide O (***ent*-1**) ($[\alpha]^{23}_D$ +65° (*c* 0.12, MeOH)), the direction of rotation is opposite to each other and the absolute value is about two times larger in our synthetic compound **1**. However, we are quite sure that the natural (+)-amphidinolide O should be ***ent*-1** again.

In conclusion, we accomplished the first convergent and enantioselective total synthesis of (−)-amphidinolide O (**1**) and P (**2**). The key reactions include enantioselective Brown allylation, *anti*- and *syn*-selective aldol reaction, (*E*)-selective olefin metathesis for the C8−C9 double bond formation, conformation-controlled stereoselective epoxidation at the C8−C9 double bond, and selective conversion of C5 ketone moieties into the exomethylene group. The absolute stereochemistry of the natural (+)-amphidinolide O (***ent*-1**) was determined unambiguously, and that of (+)-amphidinolide P (***ent*-2**) was in accord with the reported information by Trost and Williams.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) Initially, addition of $TMSCH_2Li$ to ketone **22** in THF at −78 °C was followed by Peterson olefination/hemiacetal formation in aqueous HF-CH_3CN to produce the desired (−)-amphidinolide P **2** in 13% three-step yield starting from **3**. Second, Tebbe olefination of **22** in THF at −78 °C and hemiacetal formation in aqueous HF-CH_3CN afforded the desired product **2** in 21% three-step yield starting from **3**.