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Total synthesis of amphidinolactone A and its absolute configuration

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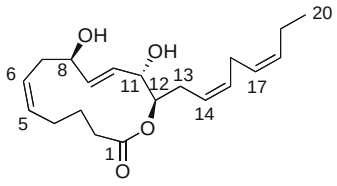
ABSTRACT

Asymmetric synthesis of amphidinolactone A, a cytotoxic macrolide from the cultured dinoflagellate *Amphidinium* sp., has been accomplished. Absolute configuration of amphidinolactone A was concluded to be **1** from comparison of the NMR data and $[\alpha]_D$ values of synthetic and natural amphidinolactone A.

Amphidinolactone A (**1**) is a cytotoxic 13-membered macrolide, which was isolated from a symbiotic dinoflagellate *Amphidinium* sp. (Y-25) separated from an Okinawan marine acoel flatworm *Amphiscolops* sp.[1] The relative stereochemistry of amphidinolactone A (**1**) has been elucidated on the basis of extensive NMR experiments.[1]



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In order to determine the absolute stereochemistry of amphidinolactone A (**1**), we planned an asymmetric total synthesis of amphidinolactone A (**1**) as shown in Scheme 1. Amphidinolactone A (**1**) could be obtained by ring-closing metathesis (RCM) of **2** through esterification of the C-1–C-5 segment (**4**) and the C-6–C-20 segment (**3**), the latter of which was derived from epoxide **5** and acetylene **6** via alkynylation of oxirane. In this Letter, we describe the total synthesis of amphidinolactone A (**1**) and its absolute configuration to be **1**.

The synthesis of the C-6–C-13 segment (**15**) of **1** is summarized in Scheme 2. 2,3-Di-*O*-cyclohexylidene-(*R*)-(+)-glyceraldehyde **7**[2] was treated with vinylmagnesium bromide to give **8** as an inseparable 5:3 diastereomeric mixture. Protection of the hydroxy group at C-11 in **8** as benzyl ether yielded **9**, which was subjected to oxidative cleavage of terminal olefin followed by Wittig reaction to provide a 4:1 (*E*:*Z*) mixture of ester (**10**). Reduction of ester **10** with DIBAL gave alcohol **11**, which was oxidized with Dess–Martin periodinane[3] and then subjected to Yamamoto's silver-catalyzed asymmetric allylation[4,5] to give a 5:3:2 mixture of **12**, **13** and *Z* isomers, respectively. At this stage, alcohols **12** and **13** were separated by silica gel column chromatography. Removal of benzyl group in **12** followed by protection of hydroxy groups provided MOM ether, which was treated with *p*-TsOH·H_2O to afford diol **14**.[6] Selective mesylation of diol **14** followed by treatment with K_2CO_3 in MeOH provided the C-6–C-13 segment (**15**).

The absolute configuration at C-8 in **12** was confirmed by a modified Mosher's method.[7] As shown in Figure 1, the values of $\Delta\delta$ [δ(*S*-MTPA ester) − δ(*R*-MTPA ester)] for H-6 and H-7 were positive, while the values of $\Delta\delta$ for H-9, H-10, H-11, H-12 and H-13 were negative, suggesting that the absolute configuration at C-8 was *R*.

To confirm the absolute configuration at C-11 in **12**, alcohol **12** was converted into **17** as follows (Scheme 3). Alcohol **12** was protected as *t*-butyldimethylsilyl ether (**16**), which was treated with Na in liq. NH_3 to provide alcohol **17**.

The absolute configuration at C-11 in **17** was elucidated by a modified Mosher's method.[7] The values of $\Delta\delta$ [δ(*S*-MTPA ester) − δ(*R*-MTPA ester)] for H-6, H-7, H-8, H-9 and H-10 were negative, while the $\Delta\delta$ values for H-12 and H-13 were positive, suggesting that the absolute configuration at C-11 was *S* (Fig. 2).

The synthesis of the C-1–C-5 segment (**4**) is summarized in Scheme 4. Commercially available alcohol **18** was treated with PDC in DMF to provide the C-1–C-5 segment (**4**). Known acetylene

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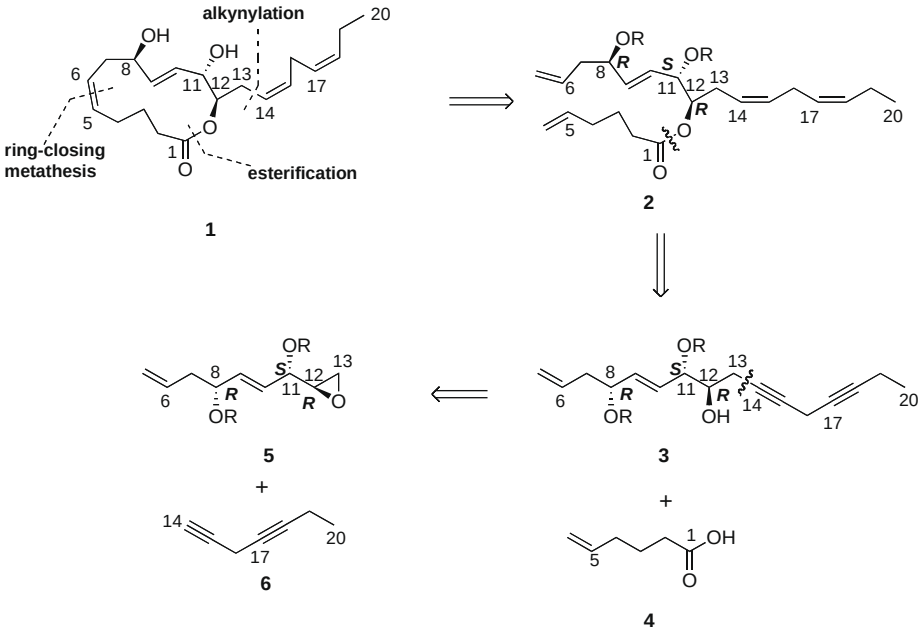
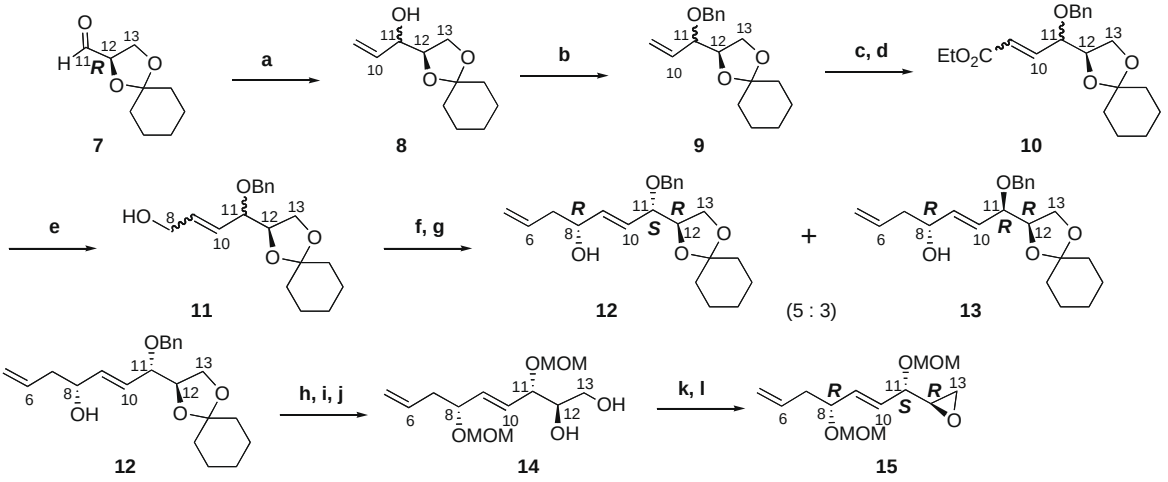


Scheme 1. Retrosynthetic analysis of amphidinolactone A (**1**).



Scheme 2. Synthesis of C-6–C-13 segment (**15**) of amphidinolactone A (**1**). Reagents and conditions: (a) CH_2=CHMgBr, THF, 0 °C, 40 min,(60%); (b) BnBr, NaH, DMF, 50 °C, 1 h, (86%); (c) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O (3:1), rt, 1 h; (d) Ph_3P=$CHCO_2Et$, CH_2Cl_2, rt, 62 h, (**10** (97%) as a 4:1 (*E*:*Z*) mixture for 2 steps); (e) DIBAL, CH_2Cl_2, −40 °C, 2 h, (80%); (f) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 30 min; (g) allyltrimethoxysilane, AgF, (*R*)-*p*-Tol-BINAP, MeOH, −20 °C, 4 h, (**12** (44%) and **13** (27%) for 2 steps, respectively); (h) Na, liq. NH_3, −78 °C, 20 min, (98%); (i) MOMCl, $^iPr_2NEt$, CH_2Cl_2, rt, 14 h (84%); (j) *p*-TsOH·H_2O, MeOH, rt, 50 min (71%); (k) MsCl, pyridine, 0 °C, 40 min and (l) K_2CO_3, MeOH, rt, 30 min (73% for 2 steps).

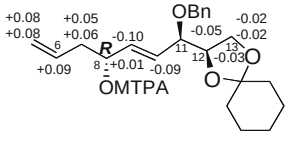
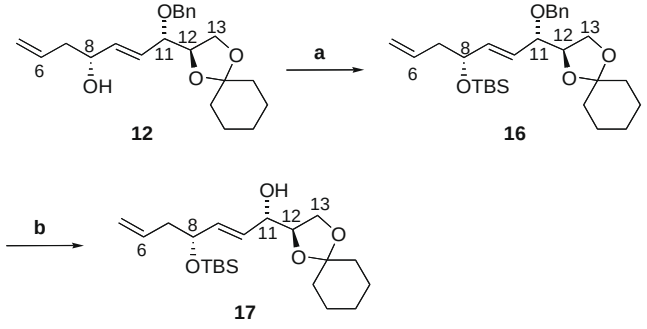
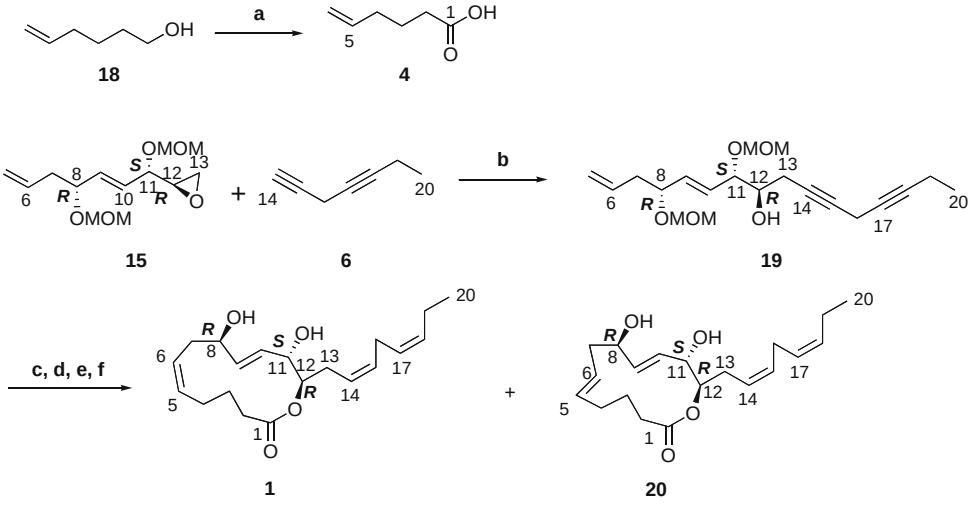


Figure 1. $\Delta\delta$ Values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA esters at C-8 of alcohol **12**.

6[8] and the C-6–C-13 segment (**15**) in hand, we turned to alkynylation of oxirane under Yamaguchi condition[9] (Scheme 4). Coupling of **15** with known acetylene **6** using *n*-BuLi and BF_3·OEt_2 provided the alcohol **19**. Reduction of **19** with hydrogen and Lindlar's catalyst followed by esterification of **4** with the alcohol using 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDC) gave ester.



Scheme 3. Conversion of alcohol **12** into alcohol **17**. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 12 h, (67%); (b) Na, liq. NH_3, −78 °C, 10 min, (82%).



Scheme 4. Alkynylation of C-6–C-13 segment (**15**) with C-14–C-20 segment (**6**) and ring-closing methathesis of **19**. Reagents and conditions: (a) PDC, DMF, rt, 7 h, (61%); (b) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF −78 °C, 20 min (99%); (c) H_2, Lindlar's Pd-cat. quinoline, benzene, rt, 13 h; (d) **4**, EDC, CH_2Cl_2, rt, 2 h; (e) Grubbs 1st generation catalyst CH_2Cl_2, 2 h and (f) *p*-TsOH·H_2O, MeOH, rt, 48 h (**1** (4%) and **20** (2%) for 4 steps, respectively).

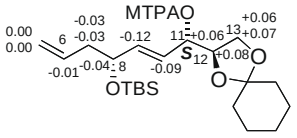


Figure 2. $\Delta\delta$ Values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA esters at C-11 of alcohol **17**.

The ester was subjected to RCM by using Grubbs' first-generation catalyst[10] followed by removal of MOM groups to furnish amphidinolactone A (**1**).[11] The synthetic material **1** was spectroscopically (IR, ^{1}H and ^{13}C NMR, HRMS)[12] identical with natural product and also had an optical rotation, $[\alpha]_D^{21}$ −65 (*c* 0.033, benzene), in good agreement with the literature value [lit.,[1] $[\alpha]_D^{19}$ −62 (*c* 0.065, benzene)]. Thus, the absolute stereochemistry of amphidinolactone A (**1**) was established as 8*R*, 11*S* and 12*R*.

Acknowledgements

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11. Because of unstability of synthetic intermediates from **19** to **1**, the yield was low.
12. **1**: colorless oil; $[\alpha]_D^{21}$ −65 (*c* 0.033, benzene); IR (film) 3390 and 1720 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 5.66 (1H, m, H-6), 5.59 (1H, m, H-15), 5.59 (1H, m, H-14), 5.54 (1H, ddd, *J* = 15.7, 7.5, 0.7 Hz, H-9), 5.46 (1H, m, H-17), 5.46 (1H, m, H-18), 5.30 (1H, ddd, *J* = 10.7, 9.6, 4.3 Hz, H-5), 5.24 (1H, ddd, *J* = 15.7, 7.5, 0.7 Hz, H-10), 5.03 (1H, ddd, *J* = 8.9, 7.6, 0.7 Hz, H-12), 4.00 (1H, m, H-8), 3.83 (1H, m, H-11), 2.88 (1H, m, H-16), 2.68 (1H, m, H-13a), 2.51 (1H, m, H-13b), 2.35 (1H, m, H-4a), 2.31 (1H, m, H-7a), 2.22 (1H, m, H-7b), 2.19 (1H, m, H-2a), 2.11 (1H, m, H-2b), 2.06 (1H, m, H-19), 1.87 (1H, m, H-4b), 1.26 (1H, m, H-3b), 0.96 (1H, t, *J* = 7.5 Hz, H-20); ^{13}C NMR (150 MHz, C_6D_6) δ 171.74, 136.68, 132.18, 131.24, 131.20, 130.74, 127.45, 125.11, 124.98, 74.00, 73.87, 72.39, 35.92, 32.07, 29.50, 26.00, 25.61, 22.96, 20.89, 14.40; ESIMS (positive) *m/z* 357 $(M+Na)^+$; HRESIMS *m/z* 357.2036 $(M+Na)^+$, calcd for $C_{20}H_{30}O_4Na$, 357.2042.
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