



## Total synthesis of amphidinolactone A and its absolute configuration

Masahiro Hangyou, Haruaki Ishiyama, Yohei Takahashi, Takaaki Kubota, Jun'ichi Kobayashi \*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

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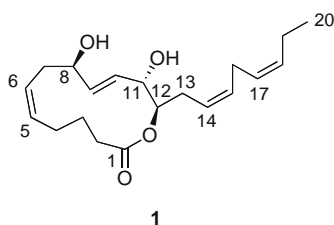
Stereochemistry

### 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.

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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 acol flatworm *Amphiscolops* sp.<sup>1</sup> The relative stereochemistry of amphidinolactone A (**1**) has been elucidated on the basis of extensive NMR experiments.<sup>1</sup>



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 alkylation 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**<sup>2</sup> 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<sup>3</sup> and then subjected to Yamamoto's silver-catalyzed asymmetric allylation<sup>4,5</sup> 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<sub>2</sub>O to afford diol **14**.<sup>6</sup> Selective mesylation of diol **14** followed by treatment with K<sub>2</sub>CO<sub>3</sub> in MeOH provided the C-6–C-13 segment (**15**).

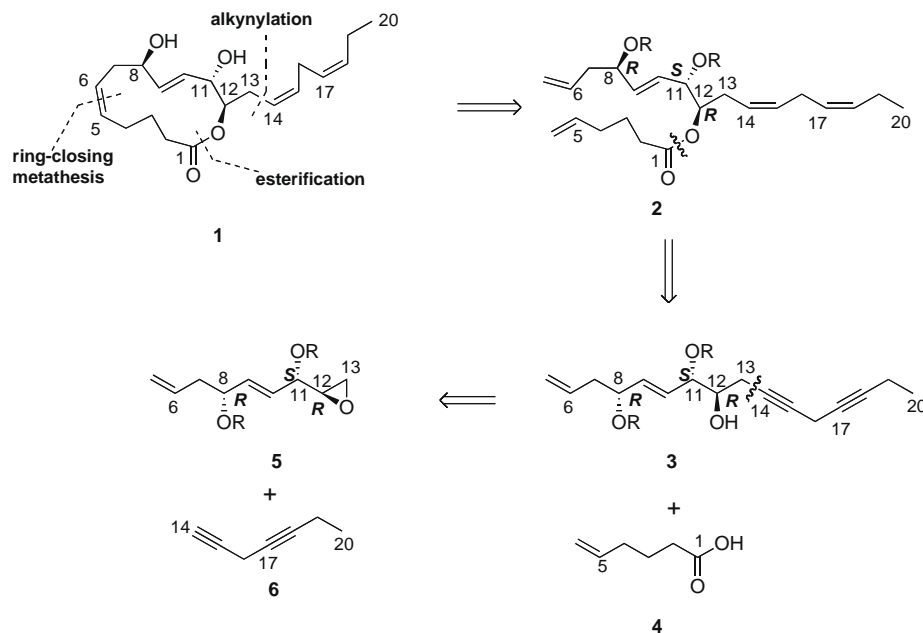
The absolute configuration at C-8 in **12** was confirmed by a modified Mosher's method.<sup>7</sup> As shown in Figure 1, the values of  $\Delta\delta$  [ $\delta$ (*S*-MTPA ester) –  $\delta$ (*R*-MTPA ester)] for H-6 and H-7 were positive, while the values of  $\Delta\delta$  for H-9, H-10, H-11, 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<sub>3</sub> to provide alcohol **17**.

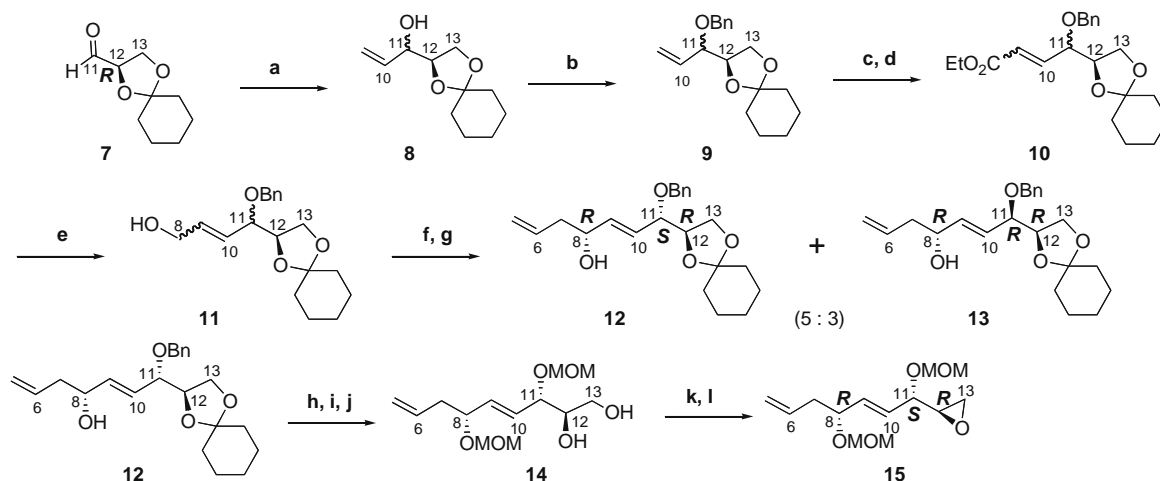
The absolute configuration at C-11 in **17** was elucidated by a modified Mosher's method.<sup>7</sup> The values of  $\Delta\delta$  [ $\delta$ (*S*-MTPA ester) –  $\delta$ (*R*-MTPA ester)] for H-6, H-7, H-8, H-9 and H-10 were negative, while the  $\Delta\delta$  values for H-12 and H-13 were positive,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

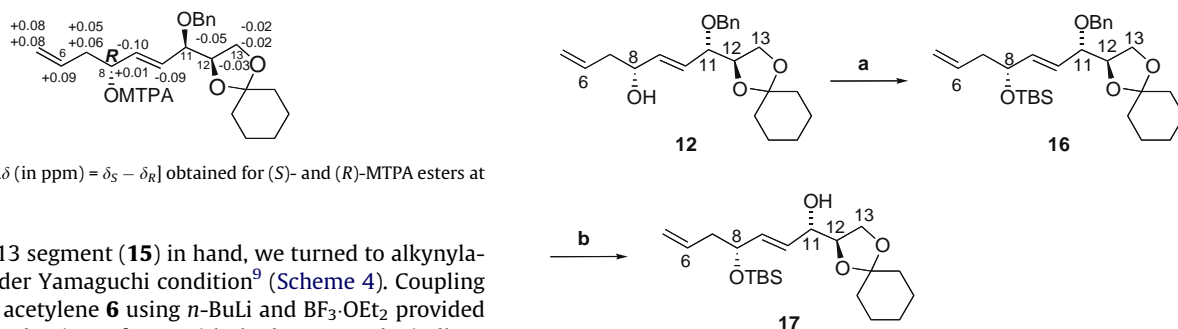
\* Corresponding author. Tel.: +81 11 706 3239; fax: +81 11 706 4989.  
E-mail address: [jkobay@pharm.hokudai.ac.jp](mailto:jkobay@pharm.hokudai.ac.jp) (J. Kobayashi).



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



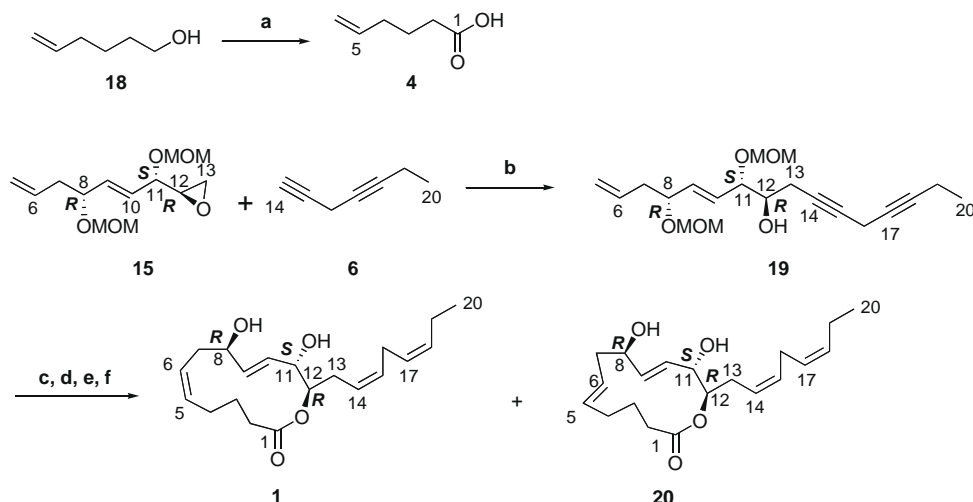
**Scheme 2.** Synthesis of C-6–C-13 segment (15) of amphidinolactone A (1). Reagents and conditions: (a)  $\text{CH}_2=\text{CHMgBr}$ , THF, 0 °C, 40 min, (60%); (b) BnBr, NaH, DMF, 50 °C, 1 h, (86%); (c)  $\text{OsO}_4$ , NaIO<sub>4</sub>, 2,6-lutidine, dioxane/H<sub>2</sub>O (3:1), rt, 1 h; (d)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 62 h, (10 (97%) as a 4:1 (E:Z) mixture for 2 steps); (e) DIBAL,  $\text{CH}_2\text{Cl}_2$ , -40 °C, 2 h, (80%); (f) Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , 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<sub>3</sub>, -78 °C, 20 min, (98%); (i) MOMCl,  $\text{Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 14 h (84%); (j) *p*-TsOH·H<sub>2</sub>O, MeOH, rt, 50 min (71%); (k) MsCl, pyridine, 0 °C, 40 min and (l)  $\text{K}_2\text{CO}_3$ , MeOH, rt, 30 min (73% for 2 steps).



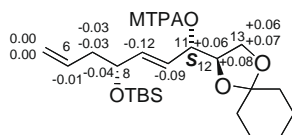
**Figure 1.**  $\Delta\delta$  Values [ $\Delta\delta$  (in ppm) =  $\delta_S - \delta_R$ ] obtained for (S)- and (R)-MTPA esters at C-8 of alcohol 12.

6<sup>8</sup> and the C-6–C-13 segment (15) in hand, we turned to alkylation of oxirane under Yamaguchi condition<sup>9</sup> (Scheme 4). Coupling of 15 with known acetylene 6 using *n*-BuLi and  $\text{BF}_3\cdot\text{OEt}_2$  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<sub>3</sub>, -78 °C, 10 min, (82%).



**Scheme 4.** Alkylation 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<sub>3</sub>·OEt<sub>2</sub>, THF –78 °C, 20 min (99%); (c) H<sub>2</sub>, Lindlar's Pd-cat. quinoline, benzene, rt, 13 h; (d) **4**, EDC, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h; (e) Grubbs 1st generation catalyst CH<sub>2</sub>Cl<sub>2</sub>, 2 h and (f) *p*-TsOH·H<sub>2</sub>O, 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<sup>10</sup> followed by removal of MOM groups to furnish amphidinolactone A (**1**).<sup>11</sup> The synthetic material **1** was spectroscopically (IR, <sup>1</sup>H and <sup>13</sup>C NMR, HRMS)<sup>12</sup> identical with natural product and also had an optical rotation, [ $\alpha$ ]<sub>D</sub><sup>21</sup> –65 (c 0.033, benzene), in good agreement with the literature value [lit.,<sup>1</sup> [ $\alpha$ ]<sub>D</sub><sup>19</sup> –62 (c 0.065, benzene)]. Thus, the absolute stereochemistry of amphidinolactone A (**1**) was established as 8*R*, 11*S* and 12*R*.

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- Keck allylation<sup>13</sup> using allyltributyltin (2 equiv) and 20 mol % catalyst prepared from Ti(*i*PrO)<sub>4</sub> and (R)-BINOL did not proceed.
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- Since removal of benzyl group proceeded in low yield at a later stage, the hydroxy groups were protected as MOM ether.
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- Because of instability of synthetic intermediates from **19** to **1**, the yield was low.
- 1**: colorless oil; [ $\alpha$ ]<sub>D</sub><sup>21</sup> –65 (c 0.033, benzene); IR (film) 3390 and 1720 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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); <sup>13</sup>C NMR (150 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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)<sup>+</sup>; HRESIMS *m/z* 357.2036 (M+Na)<sup>+</sup>, calcd for C<sub>20</sub>H<sub>30</sub>O<sub>4</sub>Na, 357.2042.
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