

Synthesis and Structure Revision of the C43–C67 Part of Amphidinol 3

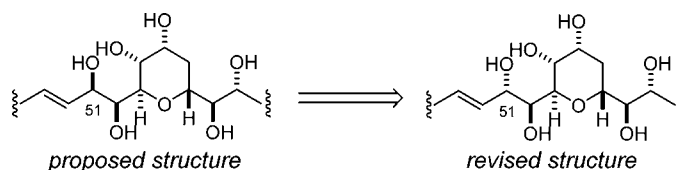
Makoto Ebine,[†] Mitsunori Kanemoto,[‡] Yoshiyuki Manabe,^{†,§} Yosuke Konno,[†]
Ken Sakai,[†] Nobuaki Matsumori,^{‡,§} Michio Murata,^{‡,§} and Tohru Oishi^{*,†}

Department of Chemistry, Faculty and Graduate School of Sciences, Kyushu University,
6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan, Department of Chemistry,
Graduate School of Science, Osaka University, 1-1 Machikaneyama, Toyonaka,
Osaka 560-0043, Japan, and JST ERATO Lipid Active Structure, 1-1 Machikaneyama,
Toyonaka, Osaka 560-0043, Japan

oishi@chem.kyushu-univ.jp

Received April 26, 2013

ABSTRACT



Stereoselective synthesis of the C43–C67 part of amphidinol 3 (AM3) and its C51-epimer was achieved starting from a common intermediate corresponding to the tetrahydropyran moiety of AM3, via asymmetric oxidations and Julia–Kocienski olefination. By comparing NMR data of the synthetic specimens with those of AM3, the absolute configuration at C51 of AM3 was revised from *R* to *S*.

Amphidinol 3 (AM3, **1**, Figure 1), produced by the dinoflagellate *Amphidinium klebsii*, elicits high antifungal efficacy with submicromolar IC₅₀ values despite its relatively potent hemolytic activity (EC₅₀ = 0.25 μM).^{1,2} These biological activities can be accounted for by formation of ion-permeable pores in a sterol dependent manner.³ The striking structural features of AM3 have attracted considerable attention from the synthetic community.^{4–9} Because of the limited availability of the natural product, and the presence of a number of stereogenic centers on the long acyclic carbon chain, it has been difficult to determine the

molecular structure of AM3. Although the stereochemistry of AM3 was determined in 1999 based on the *J*-based

[†] Kyushu University.

[‡] Osaka University.

[§] ERATO.

(1) (a) Satake, M.; Murata, M.; Yasumoto, T.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **1991**, *113*, 9859–9861. (b) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870–871. (c) Swasono, R. T.; Kanemoto, M.; Matsumori, N.; Oishi, T.; Murata, M. *Heterocycles* **2011**, *82*, 1359–1369. (d) Manabe, Y.; Ebine, M.; Matsumori, N.; Murata, M.; Oishi, T. *J. Nat. Prod.* **2012**, *75*, 2003–2006.

(2) Amphidinol congeners: (a) Paul, G. K.; Matsumori, N.; Konoki, K.; Murata, M.; Tachibana, K. *J. Mar. Biotechnol.* **1997**, *5*, 124–128. (b) Houdai, T.; Matsuoka, S.; Matsumori, N.; Murata, M. *Biochim. Biophys. Acta* **2004**, *1667*, 91–100. (c) Houdai, T.; Matsuoka, S.; Morsy, N.; Matsumori, N.; Satake, M.; Murata, M. *Tetrahedron* **2005**, *61*, 2795–2802. (d) Morsy, N.; Houdai, T.; Konoki, K.; Matsumori, N.; Oishi, T.; Murata, M. *Bioorg. Med. Chem.* **2008**, *16*, 3084–3090. (e) Swasono, R.; Mouri, R.; Morsy, N.; Matsumori, N.; Oishi, T.; Murata, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2215–2218.

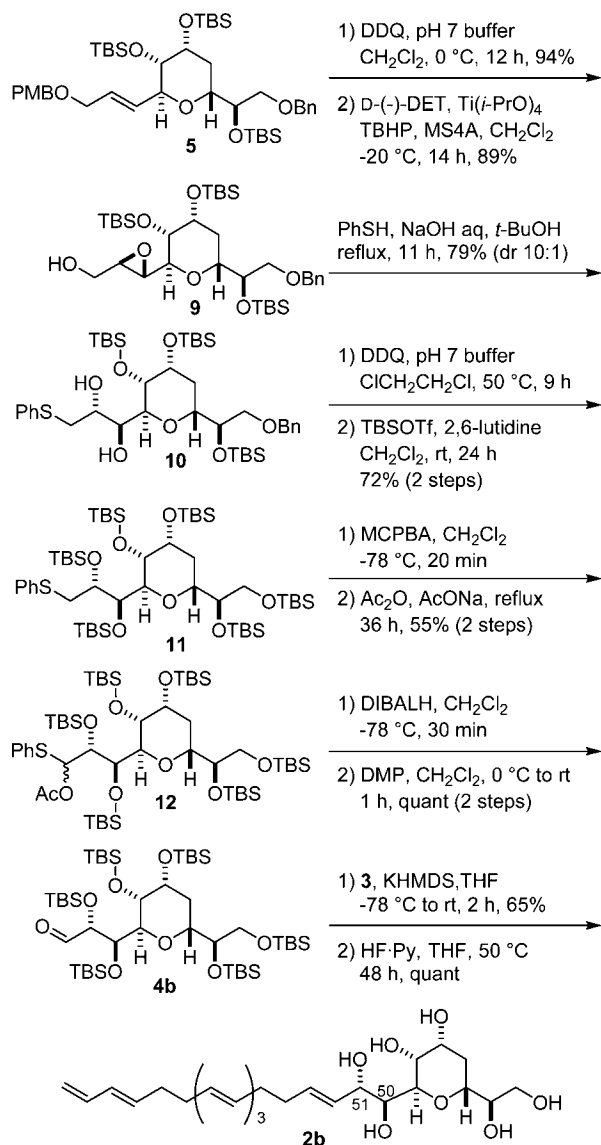
(3) (a) Echigoya, R.; Rhodes, L.; Oshima, Y.; Satake, M. *Harmful Algae* **2005**, *4*, 383–389. (b) Meng, Y.; Van Wagoner, R. M.; Misner, I.; Tomas, C.; Wright, J. L. *C. J. Nat. Prod.* **2009**, *73*, 409–415. (c) Doi, Y.; Ishibashi, M.; Nakamichi, H.; Kosaka, T.; Ishikawa, T.; Kobayashi, J. *J. Org. Chem.* **1997**, *62*, 3820–3823. (d) Kubota, T.; Tsuda, M.; Doi, Y.; Takahashi, A.; Nakamichi, H.; Ishibashi, M.; Fukushima, E.; Kawabata, J.; Kobayashi, J. *Tetrahedron* **1998**, *54*, 14455–14464. (e) Huang, X.-C.; Zhao, D.; Guo, Y.-W.; Wu, H.-M.; Lin, L.-P.; Wang, Z.-H.; Ding, J.; Lin, Y.-S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3117–3120. (f) Huang, X.-C.; Zhao, D.; Guo, Y.-W.; Wu, H.-M.; Trivellone, E.; Cimino, G. *Tetrahedron Lett.* **2004**, *45*, 5501–5504. (g) Kubota, T.; Takahashi, A.; Tsuda, M.; Kobayashi, J. *Marine Drugs* **2005**, *3*, 113–118. (h) Washida, K.; Koyama, T.; Yamada, K.; Kita, M.; Uemura, D. *Tetrahedron Lett.* **2006**, *47*, 2521–2525. (i) Van Wagoner, R. M.; Deeds, J. R.; Satake, M.; Ribeiro, A. A.; Place, A. R.; Wright, J. L. *C. Tetrahedron Lett.* **2008**, *49*, 6457–6461. (j) Huang, S.-J.; Kuo, C.-M.; Lin, Y.-C.; Chen, Y.-M.; Lu, C.-K. *Tetrahedron Lett.* **2009**, *50*, 2512–2515.

(4) (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451–1454. (b) Cossy, J.; Tsuchiya, T.; Ferrié, L.; Reymond, S.; Kreuzer, T.; Colobert, F.; Jourdain, P.; Markó, I. E. *Synlett* **2007**, 2286–2288. (c) Colobert, F.; Kreuzer, T.; Cossy, J.; Reymond, S.; Tsuchiya, T.; Ferrié, L.; Markó, I. E.; Jourdain, P. *Synlett* **2007**, 2351–2354. (d) Cossy, J.; Tsuchiya, T.; Reymond, S.; Kreuzer, T.; Colobert, F.; Markó, I. E. *Synlett* **2009**, 2706–2710.

(5) (a) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411–1414. (b) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509–5512. (c) Hicks, J. D.; Roush, W. R. *Org. Lett.* **2008**, *10*, 681–684.

(6) (a) de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853–1856. (b) de Vicente, J.; Huckins, J. R.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7258–7262. (c) Huckins, J. R.; de Vicente, J.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4757–4760.

Scheme 3. Synthesis of the C51-Epimer (**2b**)



Julia–Kocienski olefination^{16,17} of **4a** with sulfone **3**,^{6b} prepared from alcohol **7**,^{4b,6b} via Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol (**8**) and oxidation, afforded an olefin (89%, two steps) as a single geometrical isomer. Removal of all the TBS groups with HF·Py in THF at 50 °C furnished the C43–C67 part of AM3 (**2a**).

The C51-epimer (**2b**) was synthesized from the common intermediate **5** as shown in Scheme 3. Removal of the PMB group with DDQ gave an allylic alcohol (94%), which was subjected to Katsuki–Sharpless asymmetric epoxidation¹⁸ with D-(–)-diethyl tartrate (DET) to yield epoxy alcohol **9**

(16) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

(17) For recent reviews, see: (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585. (b) Aissa, C. *Eur. J. Org. Chem.* **2009**, 1831–1844.

(18) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

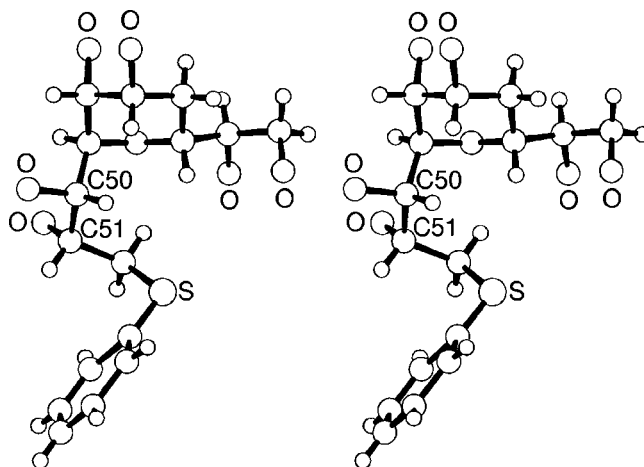


Figure 2. Stereoview for the core structure of **11** in the crystalline state, where all the *tert*-butyldimethylsilyl groups, attached to the six O atoms labeled in this figure, have been omitted for clarity.

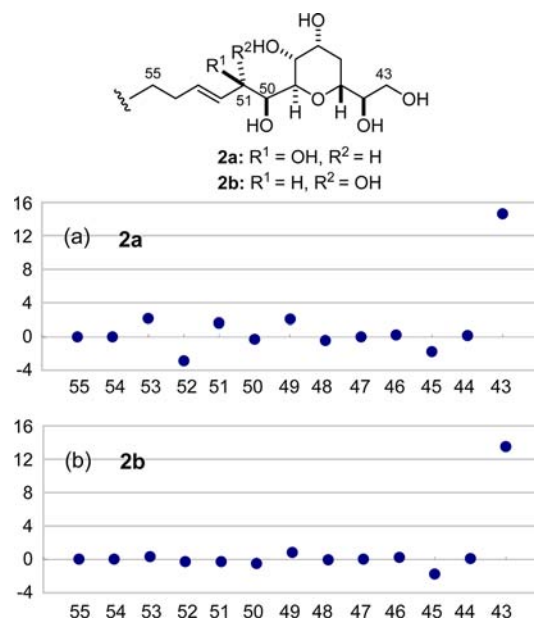


Figure 3. Differences in ¹³C NMR (150 MHz, 1:2 C₅D₅N/CD₃OD, 30 °C) chemical shifts between AM3 and the synthetic fragments (a) **2a** and (b) **2b**. The *x*- and *y*-axes represent carbon number and Δδ (Δδ = δ_{AM3} – δ_{synthetic 2} in ppm), respectively. 3.1 mg of **2a** and 4.6 mg of **2b** in 200 μL of the solvents were used.

(89%). Ring-opening of the epoxide with thiophenol via Payne rearrangement^{19,20} under basic conditions proceeded regioselectively to afford sulfide **10** with concomitant

(19) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819–3822.

(20) (a) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687–5696. (b) Ko, S. Y.; Lee, A. W.; Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. *Tetrahedron* **1990**, *46*, 245–264.

formation of an isomer in a 10:1 ratio as an inseparable mixture (79%). Slow addition of thiophenol and aqueous NaOH using a syringe pump was necessary to improve the ratio of **10**. Removal of the benzyl group with DDQ in dichloroethane in the presence of pH 7 buffer at 50 °C followed by treatment of the resulting alcohol with TBSOTf/2,6-lutidine gave **11**, which was separated from its regioisomer by silica gel column chromatography (72%, two steps). The structure of **11** was unambiguously determined by X-ray crystallography (Figure 2). Next, sulfide **11** was converted to aldehyde **4b** via (i) oxidation with *m*-CPBA giving a sulfoxide and (ii) Pummerer rearrangement^{21,22} by treatment with Ac₂O/AcONa (55%, two steps),²³ and (iii) reduction of the resulting mixed thioacetal **12** with DIBALH and oxidation of the resulting primary alcohol. In contrast to the synthesis of **2a**, Julia–Kocienski olefination of aldehyde **4b** with sulfone **3** was sluggish to furnish the corresponding olefin (65%). Removal of the TBS groups with HF·Py afforded the diastereomer at C51 of the C43–C67 part of AM3 (**2b**).

Having obtained the diastereomers corresponding to the C43–C67 part, the ¹³C NMR spectra of **2a** and **2b** were compared with those of AM3. The differences in the carbon chemical shifts of C43 to C55 between AM3, **2a** and **2b** (150 MHz, 1:2 C₅D₅N/CD₃OD) are shown in Figure 3.

The *x*- and *y*-axes represent carbon number and Δδ (Δδ = δ_{AM3} – δ_{synthetic 2} in ppm), respectively. For both diastereomers, chemical shifts at C56–C67 corresponding to the polyene moiety are identical to those of AM3, but those at the C43 terminus deviate because the structures are different from AM3. Although the deviations of **2a** at C49, C51, C52, and C53 are larger than 1 ppm, those of 51-epimer (**2b**) are almost null. These results indicate that the absolute configuration at C51 of AM3 should be revised from *R* to *S* (Figure 4).²⁴

In conclusion, stereoselective syntheses of the C43–C67 part of AM3 (**2a**) and its C51-epimer (**2b**) were achieved.

(21) (a) Pummerer, R. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282–2291. (b) Pummerer, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401–1412.

(22) For recent reviews, see: (a) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003–5034. (b) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832–5844.

(23) Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 4280–4283.

(24) In our previous study,^{1c} C51 was again assigned to be *R*. This erroneous configuration was caused by complication in ¹H signal assignment due to large chemical shift changes by peracetylation of AM3. M.M. deeply apologizes for publishing the wrong conclusion.^{1c}

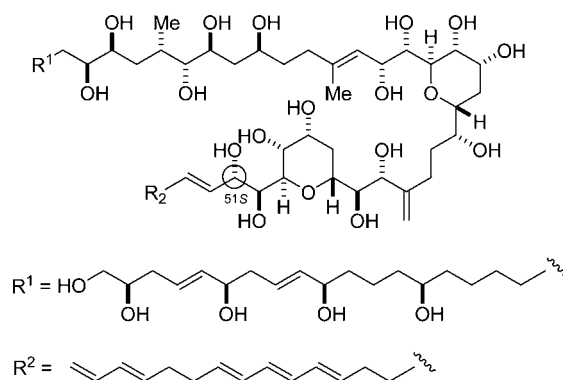


Figure 4. Revised structure of AM3.

Starting from the common intermediate **5**, the *vic*-diol moieties at C50–C51 of **2a** and **2b** were introduced by Sharpless asymmetric dihydroxylation, and Katsuki–Sharpless asymmetric epoxidation followed by epoxide opening via Payne rearrangement, respectively. The polyene part was introduced by Julia–Kocienski olefination via coupling of the aldehydes (**4a** and **4b**) with the sulfone (**3**). Judging from the comparison of ¹³C NMR data of the synthetic specimens with those of AM3, the absolute configuration at C51 should be revised to be *S*.

Acknowledgment. We are grateful to Prof. Tsutomu Katsuki and Tatsuya Uchida, Kyushu University, for measurement of mass spectra. We thank Dr. Kohei Torikai, Kyushu University, for helpful discussions. This work was supported in part by a fund from Kyushu University, Funds for the Development of Human Resources in Science and Technology originating from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and by a Grant-in-Aid for Young Scientists (B) (No. 24750092) from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available. Experimental details and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.