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

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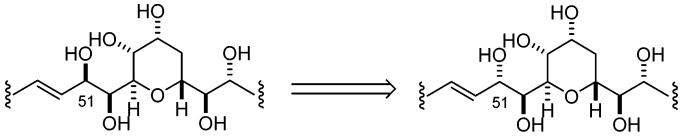
## ABSTRACT




**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 $IC_{50}$ values despite its relatively potent hemolytic activity ($EC_{50}$ = 0.25 $\mu$M).[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

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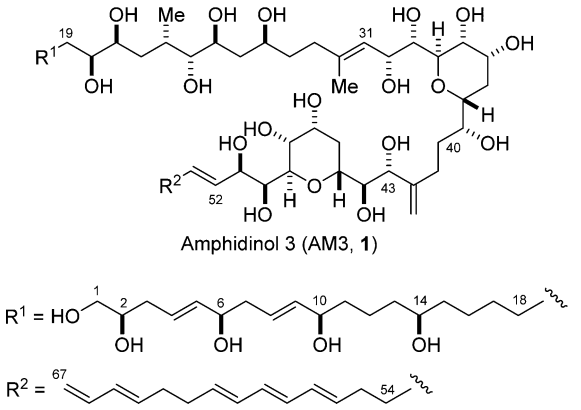
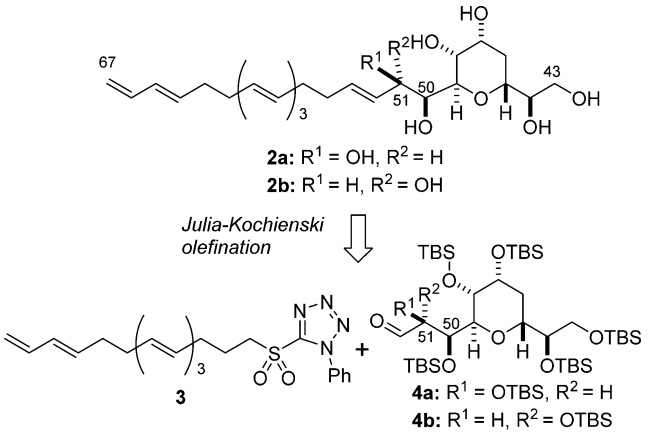


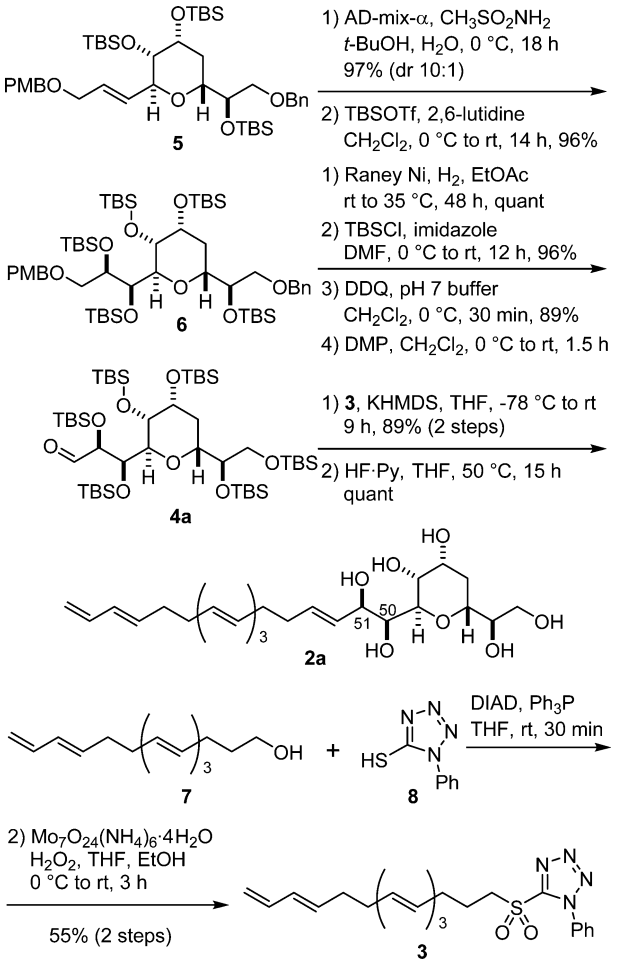

**Figure 1.** Proposed structure of amphidinol 3 (AM3, **1**).

**Scheme 1.** Synthetic Plan of the Partial Structures Corresponding to the C43−C67 Part of AM3 (**2a**) and Its C51-Epimer (**2b**)




configuration analysis (JBCA) method,[10] modified Mosher method,[11] and degradation of the natural product via oxidative cleavage, the absolute configuration at C2 was later revised to be *R* by comparing synthetic specimens with a fragment of AM3 by GC−MS.[12] The stereochemistry at C51 also remained controversial because the observed *J* values were in the intermediate range for *anti* and *gauche* conformations.[1] Therefore, chemical synthesis of the partial structure might provide clues that could confirm the stereochemistry. Herein, we report a synthesis of the C43−C67 part

**Scheme 2.** Synthesis of the C43−C67 Part of AM3 (**2a**)




of AM3 (**2a**) and its 51-epimer (**2b**), which was derived by Julia−Kocienski olefination using sulfone **3** and aldehydes **4a** and **4b** (Scheme 1). NMR spectra of **2a** and **2b** were then compared with those of the natural product.

Our synthesis of the C43−C67 part of AM3 (**2a**) is shown in Scheme 2. We previously reported a concise synthesis of the tetrahydropyran ring system corresponding to the C43−C52 part **5**,[13] a common intermediate of both **2a** and **2b**. As reported, olefin **5** was converted to **6** via Sharpless asymmetric dihydroxylation using AD-mix-α[14] (97%), followed by protection of the resulting diol as TBS ethers (96%). After protecting group manipulation, via (i) hydrogenolysis of the benzyl ether with Raney Ni (quant), (ii) protection of the resulting primary alcohol with TBSCl/imidazole (96%), and (iii) removal of the PMB group with DDQ (89%), the resulting primary alcohol was oxidized with Dess−Martin periodinane[15] to give aldehyde **4a**.

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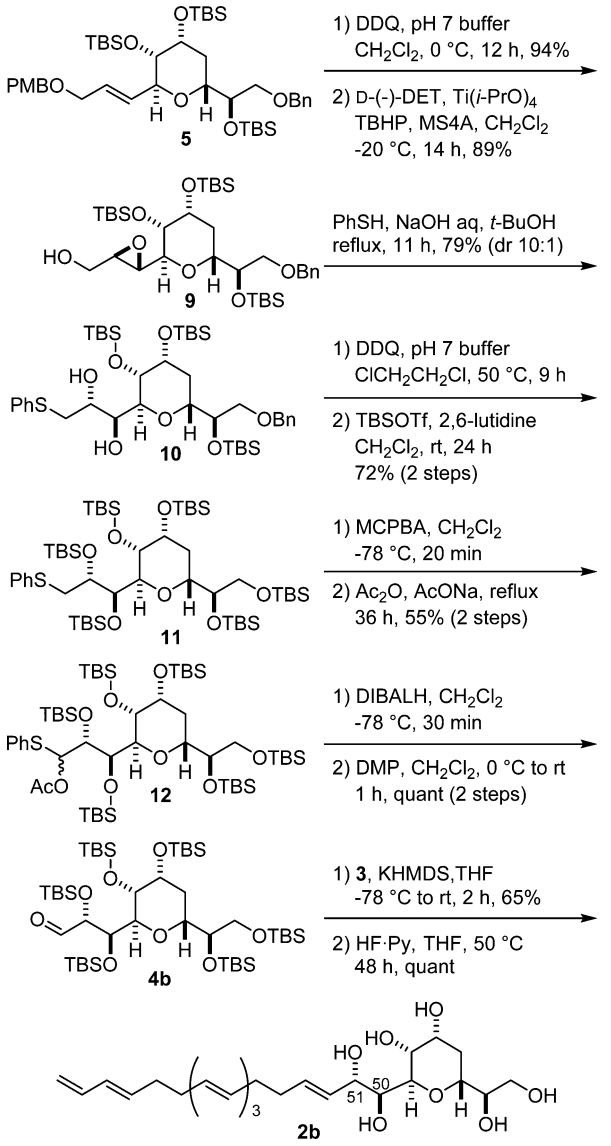
**Scheme 3.** Synthesis of the C51-Epimer (**2b**)




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 epoxidation[18] with D-(−)-diethyl tartrate (DET) to yield epoxy alcohol **9** (89%). Ring-opening of the epoxide with thiophenol via Payne rearrangement[19,20] under basic conditions proceeded regioselectively to afford sulfide **10** with concomitant

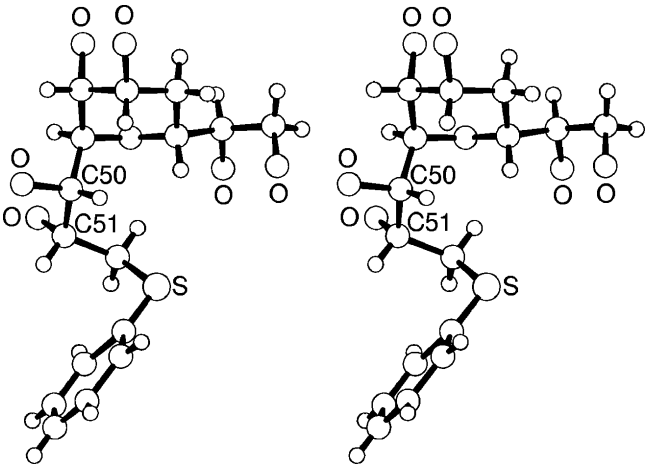



**Figure 2.** Stereoview for the core structure of **11** in the crystalline state, where all the *tert*-butyldimethysilyl groups, attached to the six O atoms labeled in this figure, have been omitted for clarity.

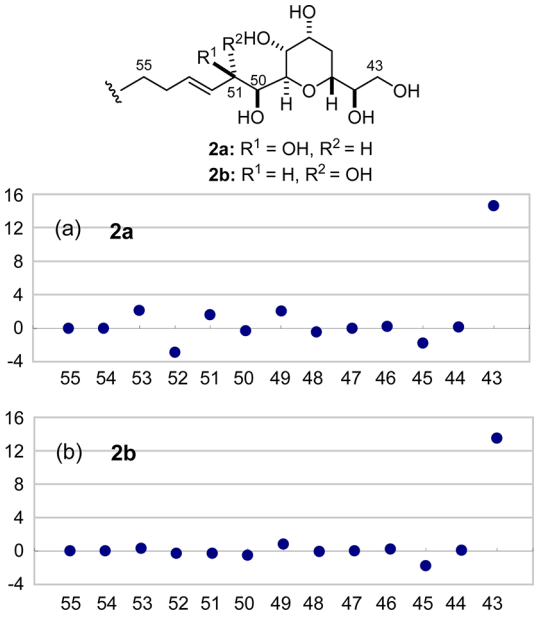



**Figure 3.** Differences in $^{13}C$ NMR (150 MHz, 1:2 $C_5D_5N$/$CD_3OD$, 30 °C) chemical shifts between AM3 and the synthetic fragments (a) **2a** and (b) **2b**. The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\Delta\delta = \delta_{AM3} - \delta_{synthetic\ 2}$ in ppm), respectively. 3.1 mg of **2a** and 4.6 mg of **2b** in 200 $\mu$L of the solvents were used.

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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 $Ac_2O$/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–Kochienski 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 $^{13}C$ 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 $C_5D_5N/CD_3OD$) are shown in Figure 3.

The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\Delta\delta = \delta_{AM3} - \delta_{\text{synthetic 2}}$ 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.

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(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]

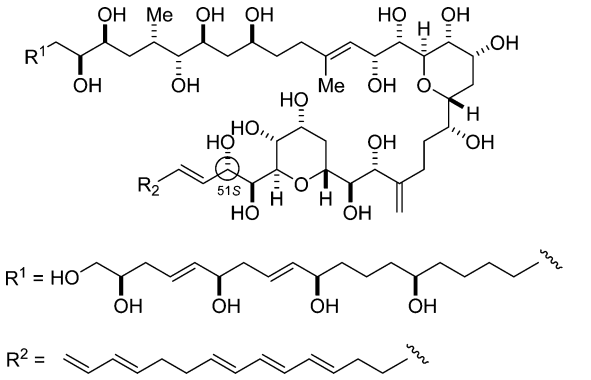


**Figure 4.** Revised structure of AM3.

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 epoxydation 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 $^{13}C$ NMR data of the synthetic specimens with those of AM3, the absolute configuration at C51 should be revised to be *S*.

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**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.