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Combinatorial Synthesis of the 1,5-Polyol System Based on Cross Metathesis: Structure Revision of Amphidinol 3

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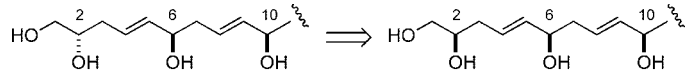
ABSTRACT



originally proposed structure *revised structure*

Combinatorial synthesis of a 1,5-polyol system corresponding to the C1−C14 unit of amphidinol 3 (AM3) and its diastereomers was achieved via chemoselective cross metathesis as the key step. Comparison of ^{13}C NMR data of the synthetic specimens with that of AM3 led to a controversy regarding the originally proposed structure. From GC-MS analysis of the degradation product, the absolute configuration at C2 of AM3 has been revised to be *R*.

Marine dinoflagellates are a rich source of biologically and structurally unique secondary metabolites.[1] Amphidinols (AMs) were isolated from the dinoflagellate *Amphidinium klebsii*, which elicit potent antifungal and hemolytic activity.[2] The biological activities can be accounted for by the formation of ion-permeable pores in a sterol-dependent manner.[3] AMs comprise a hydrophobic polyene unit and a hydrophilic part containing acyclic polyol and substituted tetrahydropyran rings, in which structural diversity is mainly focused on the polyol unit. Amphidinol 3 (AM3, **1**, Figure 1) is the most potent antifungal among the AMs, and the absolute configuration was elucidated by extensive NMR analysis based on the JBCA method,[4] modified Mosher method,[5] and HPLC analysis of the degradation products.[6] The striking structural feature of AM3 has attracted considerable attention from the synthetic community, and a number of synthetic studies have been reported by the Cossy,[7] Roush,[8] Rychnovsky,[9] Paquette,[10] and Markó[11] groups. During the course of our mode-of-action studies of AMs,[12] it was revealed that the structural difference of the polyol domain and the terminal olefin moiety modulate the potency

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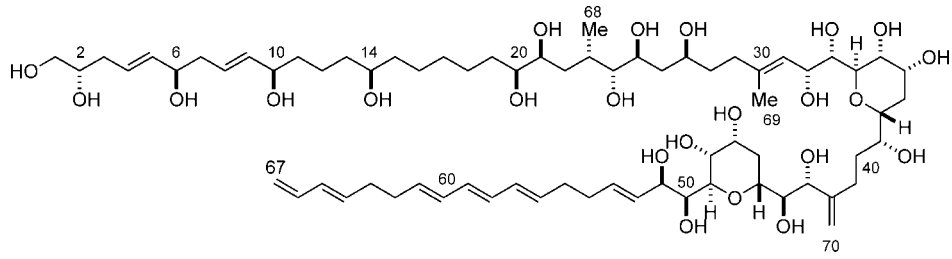
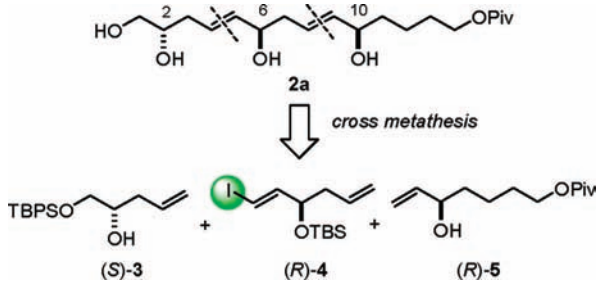


Figure 1. Originally proposed structure of amphidinol 3 (AM3, **1**).

of the biological activity, and it is of interest whether the absolute configuration of the acyclic polyol domain of AM3 has an effect on the biological activity. Herein, we report a combinatorial synthesis of the 1,5-polyol unit corresponding to the C1−C14 moiety of AM3 and its diastereomers via chemoselective cross metathesis as the key step, which has resulted in the structure revision of AM3.

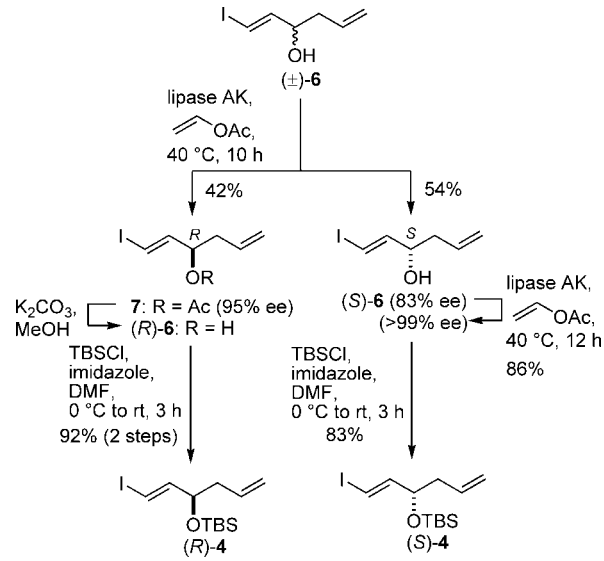
Scheme 1. Synthesis Plan



Although syntheses of the 1,5-polyol system of AM3 have been reported[7−10] using asymmetric allyltitanation,[13] double allylboration,[14] and Julia−Kocienski olefination,[15] we envisaged a versatile synthetic route to the C1−C14 segment (**2a**) of AM3 that could readily provide all diastereomers via successive coupling of the building blocks equipped with defined stereogenic centers (Scheme 1). In this strategy, diene (*R*)-**4** was envisioned as a key intermediate, in which the iodoolefin is regarded as a protected terminal olefin for chemoselective cross metathesis with (*R*)-**5**, and the iodoolefin moiety was to be converted to a terminal olefin afterward by reductive removal of the iodide for subsequent cross metathesis with (*S*)-**3**. On the basis of this strategy, all stereoisomers could be synthesized by utilizing each enantiomer of the building blocks.

Although enantioselective synthesis of the related compound of (*R*)-**4** has been reported by Trost[16] using Brown asymmetric allylation[17] and by Kobayashi[18] using Sharpless epoxidation,[19] we developed a versatile method, which provides both enantiomers in large quantities, using lipase-catalyzed kinetic resolution (Scheme 2).[20] Racemic alcohol (±)-**6**[21] (29.3 g) was treated with 10% w/w lipase AK (Amano) in vinyl acetate at 40 °C for 10 h to furnish acetate

Scheme 2. Preparation of (*R*)- and (*S*)-**4**



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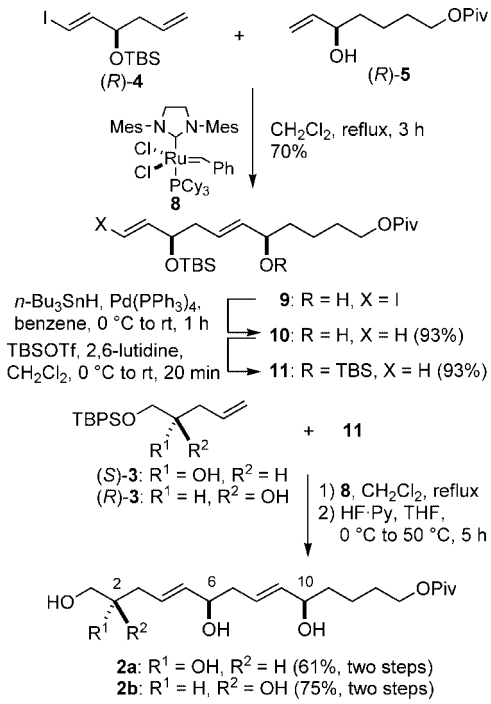
Scheme 3. Synthesis of **2a** and Its C2 Epimer **2b**



7 (42%, 95% ee) and alcohol (*S*)-**6** (59%, 83% ee). The optical purity of (*S*)-**6** was improved to >99% ee by retreatment with lipase AK. The optical purity was determined by HPLC analysis using a chiral column, and the absolute configuration was confirmed by the modified Mosher method.[22] In an analogous sequence, building block (*R*)-**5** was synthesized (98% ee) via kinetic resolution of (±)-**5**.[22]

Synthesis of the C1−C14 segment (2*S*,6*R*,10*R*)-**2a** commenced with cross metathesis of (*R*)-**4** using 3 equiv of (*R*)-**5** by the action of Grubbs second-generation catalyst **8**.[23] As expected, chemoselective cross coupling between the terminal olefins was successfully achieved in the presence of iodoolefin to afford diene **9** in 70% yield (>*E*:*Z* = 10:1), presumably due to the steric hindrance of the iodoolefin moiety. Reductive removal of the iodide with Bu_3SnH in the presence of $Pd(PPh_3)_4$[24]was followed by protection of the secondary alcohol with TBS ether to provide **11**. Subsequent conventional cross metathesis with 3 equiv of (*S*)-**3**[25] derived from (*R*)-glycidol proceeded smoothly to afford the diene (>*E*:*Z* = 10:1), while that with the counterpart **10** resulted in the formation of byproduct, due to cross metathesis with the internal olefin. Removal of all silyl groups with HF·Py afforded (2*S*,6*R*,10*R*)-**2a**. On the other hand, cross metathesis of **11** with (*S*)-**3** followed by removal of the silyl groups furnished (2*R*,6*R*,10*R*)-**2b** (Scheme 3). In an analogous sequence, other diastereomers (2*S*,6*S*,10*R*)-**2c** and (2*R*,6*S*,10*R*)-**2d** were also synthesized.[22]

Having obtained the diastereomers corresponding to the C1−C14 moiety, NMR spectra of **2a**∼**2d** were compared with those of AM3. ^{1}H NMR spectra were virtually indistinguishable among the diastereomers with respect to

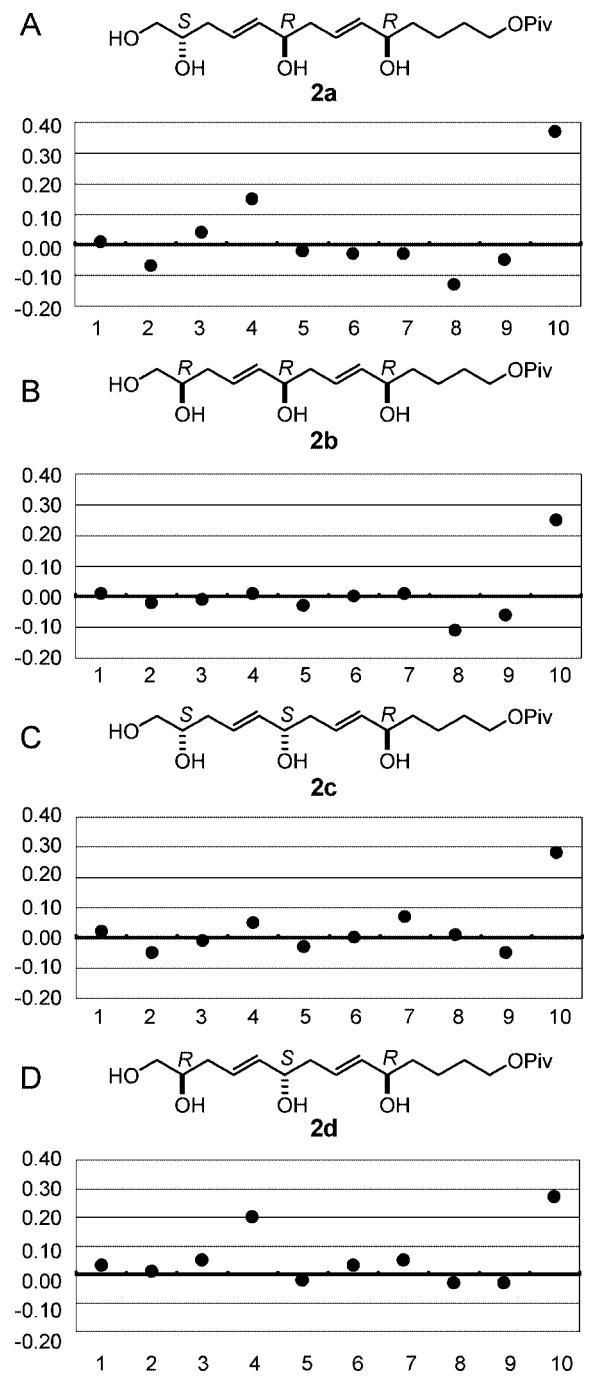


Figure 2. Differences in carbon NMR (125 MHz, 1:2 C_5D_5N/CD_3OD, 30 °C) chemical shifts between AM3 and the synthetic fragments (**2a**∼**2d**). The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\Delta\delta = \delta$AM3 − δsynthetic **2** in ppm), respectively.

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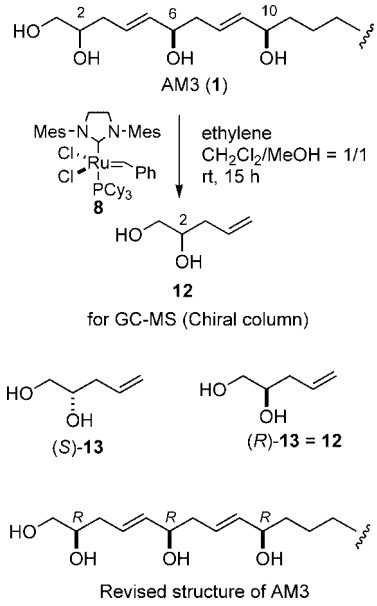
either chemical shift or *J*-coupling patterns, due to the remote (1,5-) stereogenic centers.[26] The differences in the carbon chemical shifts of C1 to C9 between AM3 and **2a**∼**2d** (125 MHz, 1:2 C_5D_5N/CD_3OD, 30 °C)[4] were also insignificant and within 0.2 ppm, as shown in Figure 2. However, the deviations at C4 of the 2,6-*syn* isomers (**2b** and **2c**) appeared to be lower than those of the 2,6-*anti* isomers (**2a** and **2d**). Since the absolute configurations at C6 and C10 in AM3 (**1**) were determined to be (6*R*, 10*R*) by the modified Mosher method, the stereochemistry at C2 became controversial.

Scheme 4. Degradation of AM3



Therefore, it was decided to reconfirm the absolute configuration at C2. Although degradation of AM3 was previously carried out via oxidative cleavage of the double bond (C4−C5) in three steps and the product was analyzed by HPLC with UV detection,[6] we envisaged a single-step manipulation using olefin metathesis[27] because of the limited availability of the natural product. For unambiguous identification of the minute degradation product, a GC-MS instrument equipped with a chiral capillary column (Varian CP-Chirasil-DEX CB) was used according to the procedure applied in the case of maitotoxin.[28] As shown in Scheme 4, a solution of AM3 (ca. 50 μg, estimated by the ε value from the UV spectra) in 1:1 CH_2Cl_2/MeOH was treated with Grubbs catalyst **8** in the presence of ethylene for 15 h at room temperature, and the product **12** was analyzed by GC-MS.[22] Retention times of the authentic samples (*S*)-**13** and (*R*)-**13** were 9.84 and 9.90 min, respectively, and that of the degradation product **12** was identical with (*R*)-**13**, indicating that the absolute configuration at C2 is *R*.

The reason for the misassignment in the original configuration is unclear. One of the possible explanations is that the sample for HPLC analysis was contaminated with ozonolysis products derived from the other portions of AM3. One of these fragments exhibited a peak with a retention time similar to that of the synthetic enantiomer of 1,2,4-butanetriol, while the fragment from the natural product provided no detectable peak due to the small sample size subjected to the degradation reaction sequence including three steps of derivatization.[6]

In conclusion, a practical method for the synthesis of chiral building blocks (*R*)- and (*S*)-**4** and (*R*)- and (*S*)-**5** was developed via lipase-catalyzed kinetic resolution. Combinatorial synthesis of the 1,5-polyol system of AM3 was achieved based on cross metathesis of the building blocks, in which iodoolefin was utilized as a masked terminal olefin. From the comparison of ^{13}C NMR data of the synthetic specimens with those of AM3, and by GC-MS analysis of the degradation product, the absolute configuration at C2 has been revised to be *R*.

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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.

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