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SYNTHESIS OF AN ANALOG OF AMPHIDINOL 3 CORRESPONDING TO THE C31–C67 SECTION

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Abstract – An artificial analog corresponding to the C31–C67 section of amphidinol 3 (AM3) was designed as a part of the structure–activity relationship studies to elucidate structure requirements for eliciting antifungal activity. To reduce the number of synthetic steps, the 43-deoxy-51-epi derivative containing common tetrahydropyran ring system was designed and synthesized from a pivotal intermediate in 17 steps. The analog elicited no antifungal activity, suggesting that not only the two tetrahydropyran rings, but also polyol section of AM3 are necessary to elicit antifungal activity.

Dinoflagellates are rich source of biologically active natural products such as amphidinol 3 (AM3, Figure 1)[1] and its congeners including karlotoxin 2 (KmTx2, Figure 2).[2] The structural feature of AM3 is represented by the presence of the hydrophilic polyol section, two tetrahydropyran (THP) rings, and the hydrophobic polyene moiety. AM3 elicits antifungal activity. It is reported that the hydrophobic polyene section of AM3 is inserted into the lipid bilayer membrane, and intramolecular hydrogen bond stabilizes hairpin conformation. Molecular assemblage of AM3 resulted in the formation of pore to increase membrane permeability.[3] A number of synthetic studies of AM3 including designed analogs have been reported,[4-10] and structure of AM3 has recently been revised as shown in Figure 1.[10g]

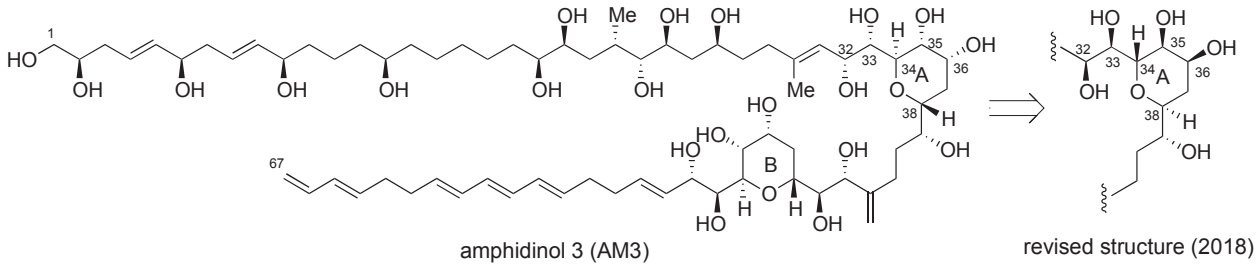


Figure 1. Structure of amphidinol 3 (AM3) and revised structure in 2018

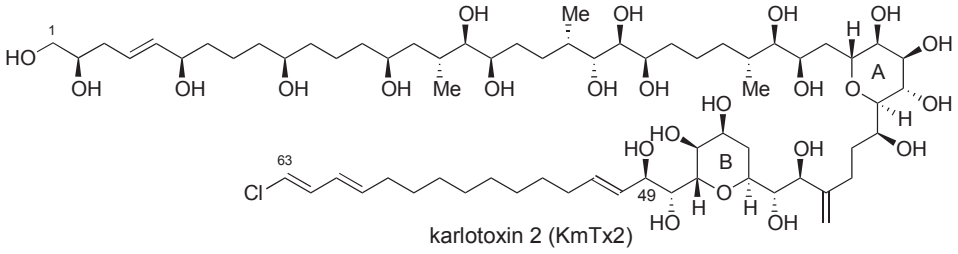


Figure 2. Structure of karlotoxin 2 (KmTx2)

As a part of our program to elucidate minimum structural requirements for eliciting antifungal activity, artificial analogs corresponding to the C43–C67 section of AM3 (AMQ-10, **1**)[10d] and the C21–C39/C52–C67 portion of AM3 (AMQ-20, **2**) were synthesized and the antifungal activity was evaluated (Figure 3).[10f] However, both of them were not active, suggesting that presence of both THP rings are important to elicit antifungal activity.

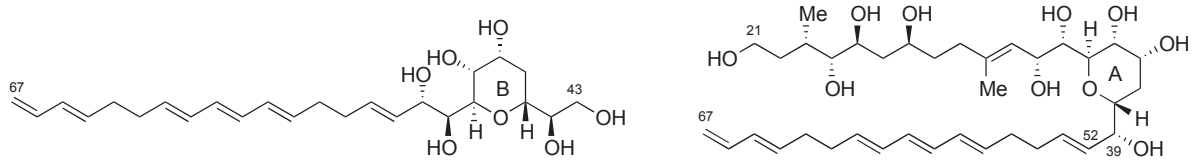
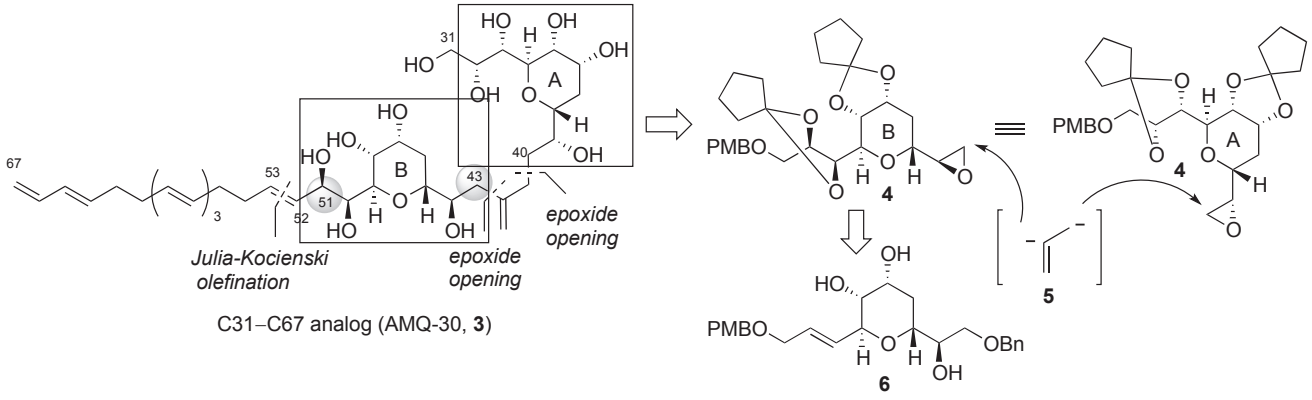


Figure 3. Structures of the C43–C67 section of AM3 (AMQ-10, **1**), truncated AM3 analog corresponding to the C21–C39/C52–C67 section (AMQ-20, **2**)

Herein, we designed advanced analog corresponding to the C31–C67 section of AM3 (AMQ-30, **3**) containing common A- and B-rings (lacking the hydroxy group at C43 with opposite absolute configuration at C51) to reduce the number of synthetic steps (Scheme 1).[11] It is intriguing whether the analog **3** lacking the polyol section elicits antifungal activity. The designed analog **3** would be synthesized via Julia–Kocienski olefination[12] to introduce the polyene side chain, and the bis-THP moiety would be constructed through the sequential coupling of the common intermediate **4** corresponding to both the A- and B-ring with carbanion equivalent **5**. The epoxide **4** could be synthesized from the known compound **6**[10b] as a common intermediate.

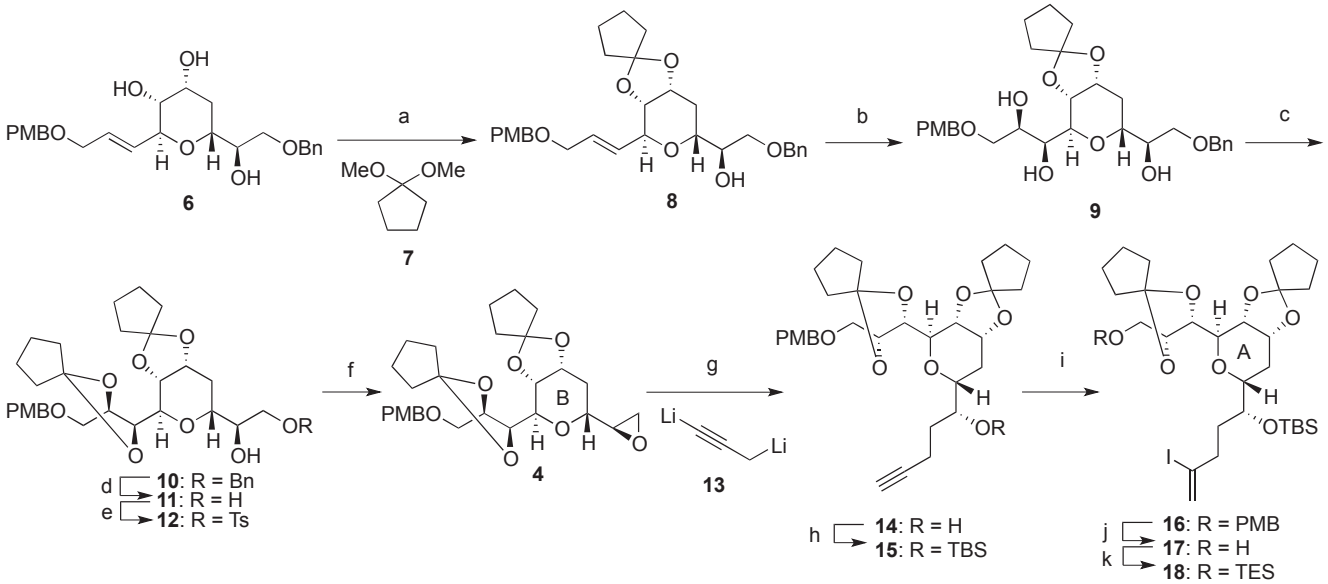
Synthesis of the A- and B-ring fragments is shown in Scheme 2. Protection of the *cis*-diol **6** as cyclopentylidene acetal by treatment with 1,1-dimethoxycyclopentane **7** in the presence of PPTS provided **8** (88%). Sharpless asymmetric dihydroxylation[13] of the olefin **8** furnished *cis*-diol **9** (97%), which was also protected as cyclopentylidene acetal to afford **10** (95%). Selective hydrogenolysis of the Bn group of **10** in the presence of PMB group was achieved by using Raney Ni (W-2) under a hydrogen atmosphere to furnish diol **11** (quant). Selective tosylation of the primary alcohol **11** by treatment with TsCl in the presence of Bu_2SnO[14] provided monotosylate **12** (73%) with recovery of **11** (24%). Treatment of **12** with

K_2CO_3 afforded epoxide **4** (94%).



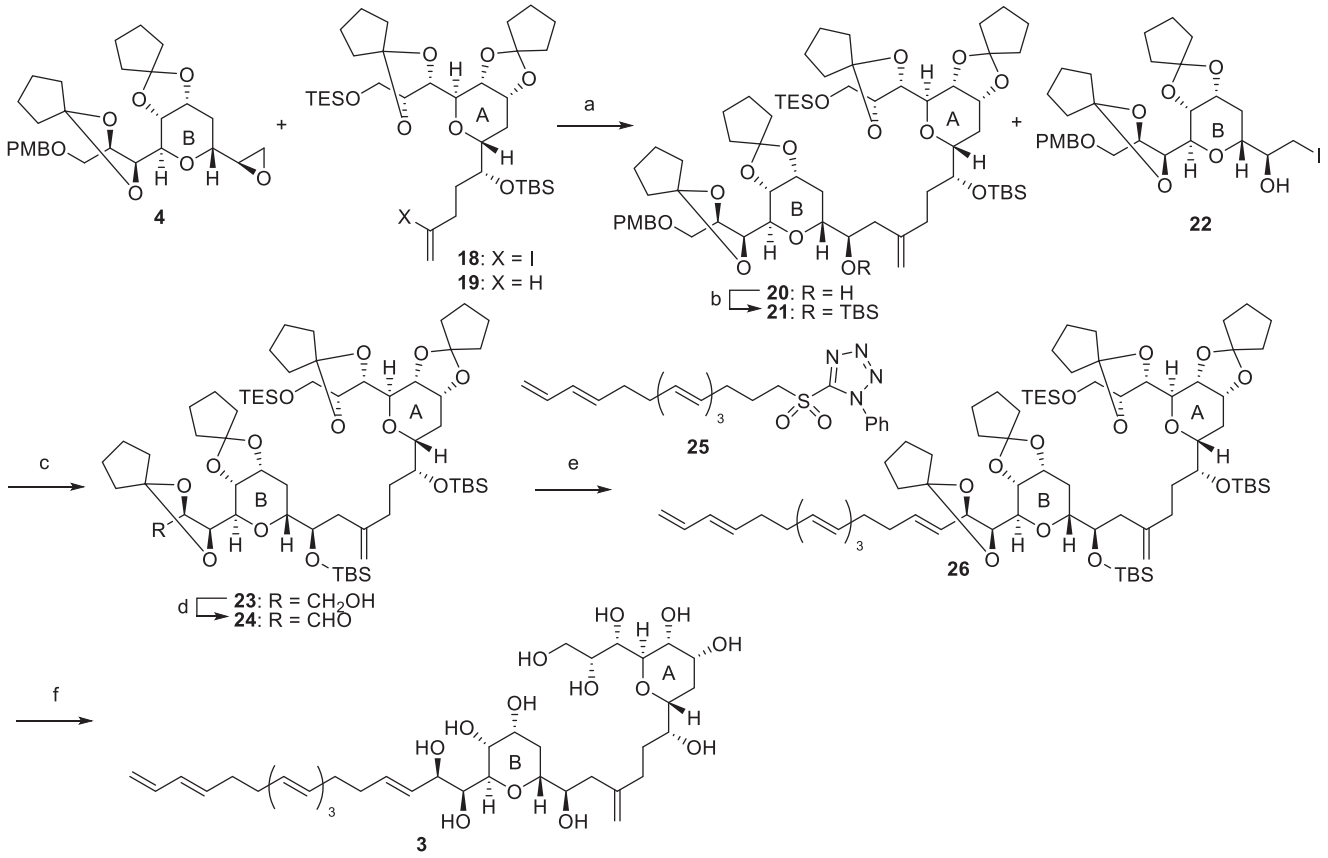
Scheme 1. Synthesis plan of the analog corresponding to the C31–C67 section of AM3 (AMQ-30, **3**)

Then, conversion of the B-ring fragment **4** to the A-ring fragment **18** was investigated. According to the procedure reported by Cabezas,[15] epoxide **4** was treated with dilithium reagent **13** generated from allene and *n*-BuLi to afford **14** (93%). The resulting secondary alcohol was protected as TBS ether to afford terminal alkyne **15** (quant). Ni-Catalyzed regioselective hydroalumination[16] of the alkyne **15** followed by iodination furnished iodoolefin **16** (88%) as an inseparable mixture with the regioisomer (*E*-iodoolefin) in a 5:1 ratio. After removal of the PMB group with DDQ, undesired isomer was separated to afford the pure alcohol **17** (68%), which was protected as a TES ether to furnish the A-ring fragment **18** (98%).



Scheme 2. Reagents and conditions: (a) **7**, PPTS, CH_2Cl_2, rt, 30 min, 88%; (b) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, 6 h, 97%; (c) **7**, PPTS, CH_2Cl_2, rt, 1 h, 95%; (d) Raney Ni (W-2), EtOH, rt, 27 h, quant; (e) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, rt, 12 h, 73% (24% recovery of **11**); (f) K_2CO_3, MeOH, CH_2Cl_2, rt, 1 h, 94%; (g) **13**, hexane, Et_2O, −78 to −20 °C, 2 h, 93%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 to 0 °C, 1.6 h, quant; (i) $Ni(dppp)Cl_2$, DIBALH, 0 °C, then NIS, THF, 0 °C, 1 h, 88% (**16**:regioisomer = 5:1); (j) DDQ, pH 7 buffer, CH_2Cl_2, rt, 4 h, 68%; (k) TESCl, NaH, THF, −20 to 0 °C, 1 h, 98%.

With the A-ring and the B-ring in hand, synthesis of the analog **3** was carried out (Scheme 3). Coupling reaction of the epoxide **4** and the alkenyl iodide **18** was examined in a similar manner as reported by Kishi and Pattenden.[17] According to the procedure reported by Lipshutz,[18] iodide **18** was treated with *t*-BuLi followed by 2-ThCu(CN)Li, and the resulting higher-order cuprate was reacted with epoxide **4** to give coupling product **20** (24%) with concomitant formation of terminal olefin **19** (49%). To activate the reactivity of epoxide **4**, $BF_3{\cdot}OEt_2$ was added to the reaction mixture to afford **20** (32%) with concomitant formation of olefin **19** (49%) and iodohydrin **22** (40%). Although the yield of the coupling product should be improved, we set for the further transformations. The secondary alcohol **20** was protected as TBS ether **21** (99%), and removal of the PMB group (92%) followed by Swern oxidation of the primary alcohol **23** furnished aldehyde **24**. Julia–Kocienski olefination[12] of the aldehyde **24** and sulfone **25**[10f] by the treatment of KHMDS in THF to afford olefin **26** as a mixture of *E*- and *Z*-isomer in a 2:1 ratio. The global deprotection with HF·pyridine in THF followed by addition of MeOH at 50 °C afforded the designed analog **3** (7%, for three steps) after purification by HPLC. The total number of steps to synthesize **3** (MW 724.89) from **6** is 17.



Scheme 3. Reagents and conditions: (a) **18**, *t*-BuLi, THF, −78 °C, 10 min, then 2-ThCu(CN)Li in THF, −78 °C, 1 h, −20 °C, 30 min, then **4**, $BF_3{\cdot}OEt_2$, THF, −78 °C, 15 min, 32% (**19**: 49%, **22**: 40%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 to 0 °C, 1.6 h, 99%; (c) DDQ, pH 7 buffer, CH_2Cl_2, rt, 4 h, 92%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h; (e) **25**, KHMDS, toluene, THF, −78 °C to rt, 21 h (*E*/*Z* = 2:1); (f) HF·pyridine, THF, 50 °C, 2.5 d, then MeOH, 50 °C, 8.5 d, 7% (after HPLC purification for three steps).

Although antifungal activity of the synthesized analog **3** against *Aspergillus niger* was evaluated by paper disk method, **3** was not active (>100 μg/disk), suggesting that not only the bis-THP system but also the polyol section would be important to elicit antifungal activity, while the difference in the structure (antipodal A-ring and 43-deoxy-51-epi) is to be also considered.

In conclusion, we have synthesized the analog of AM3 corresponding to the C31–C67 section (**3**) via successive coupling of the common epoxides **4** (the A- and B-rings) and Julia–Kocienski olefination as key steps. Further structure–activity relationship studies of AM3 based on the chemical synthesis of partial structures are currently in progress in our laboratory.

ACKNOWLEDGEMENTS

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