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1. Synthesis of the common C.1-C.13 hydrophobic domain of the B-type amphidinolides

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Abstract: In this letter, the first of two in this issue, we describe the synthesis of the C.1-C.13 hydrophobic domain common to the B-type amphidinolides.

The amphidinolides are a family of cytotoxic marine metabolites isolated from the dinoflagellate *Amphidinum* sp. collected principally from the waters near Okinawa as well as near St. Thomas, U.S. Virgin Islands.[2] Among the known amphidinolides, whose members now number over eighteen, are the potent B-type amphidinolides B1, B2, B3, D, G, H, and L (Figure 1). These structurally related macrolides display a unique arrangement of functionality, including a relatively oxygenated hydrophilic domain and a sparsely functionalized, epoxide-containing hydrophobic domain.

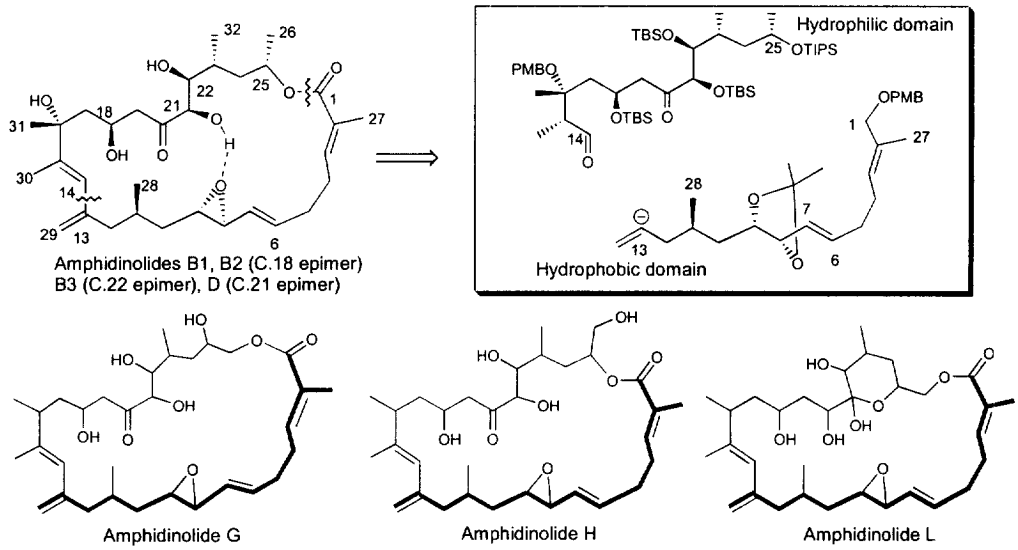

Figure 1. The B-type amphidinolides. Hydrophobic domains are highlighted in bold.

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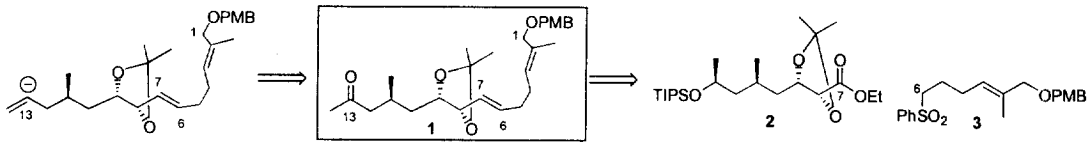
In 1994, Clardy and Shimizu published a single X-ray crystal structure of amphidinolide B1 that revealed an apparent 2Å intramolecular hydrogen bond between the epoxide on the hydrophobic domain and the C.21 hydroxyl group on the hydrophilic domain.[3] This novel interaction is particularly interesting in light of the fact that methanolysis of the epoxide at C.8 during isolation of the molecule gave a methyl ether that was only 1/100th as active.[4]

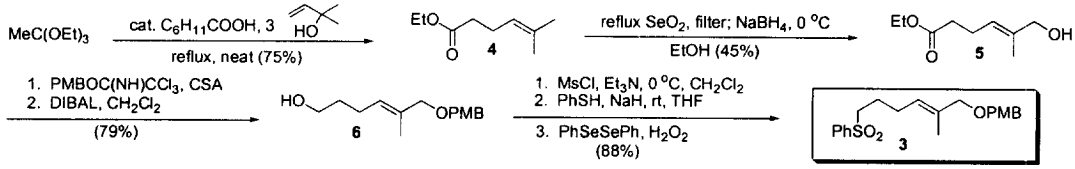
The absolute stereochemistry of amphidinolide B1 has since been determined and a number of groups have reported partial syntheses that address every portion of this molecule with the exception of the diene moiety.[5-10] Our retrosynthetic analysis of the B-type amphidinolides reflects our desire to devise a synthetic route that would allow us to access all seven members (see inset, Fig. 1). Thus, disconnections at the diene and at the lactone ester partition the molecule into a *variable* hydrophilic domain aldehyde and a *common* C.1-C.13 vinyl anion. In this letter we describe the synthesis of the common C.1-C.13 hydrophobic domain of the B-type amphidinolides. Syntheses of the hydrophilic domain aldehyde specific to amphidinolide B1 and the diene moiety and will be presented in the following letter.

We identified methyl ketone **1** as a versatile precursor to the C.13 vinyl anion synthon (Scheme 1) *via* intermediates such as hydrazones, vinyl triflates, and vinyl iodides. It was anticipated that the vinyl epoxide would be particularly labile, requiring that it be installed late in the synthesis. A particularly appealing strategy was storage of the epoxide as a *syn*, 1,2-diol that can be converted later to the epoxide with net retention of configuration at both stereocenters.[11] Disconnection of the *E*-alkene *via* a Trost/Julia olefination sequence led to ester **2** and achiral sulfone **3**.[12]



Scheme 1. Retrosynthesis of the common hydrophobic domain.

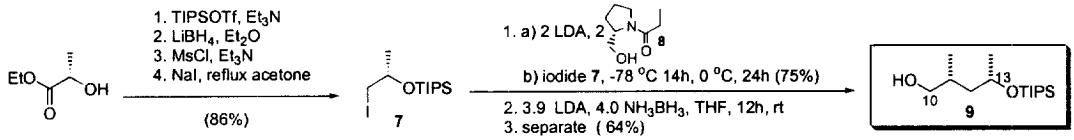
The synthesis of sulfone **3** began with ester **4**, prepared in bulk from commercially available 2-methyl-3-buten-2-ol *via* a [3,3] sigmatropic rearrangement with triethyl orthoacetate. Allylic oxidation of the *trans* methyl group in **4** with selenium dioxide gave, following reductive workup to remove any overoxidized enal, the desired *E*-allylic alcohol **5**. Protection of alcohol **5** and reduction of the ester moiety proceeded in excellent yield to provide alcohol **6**. Conversion of the alcohol to sulfone **3** was achieved *via* a short series of operations culminating in a selenium-mediated chemoselective sulfide oxidation.[13]



Scheme 2. Synthesis of C.1-C.6 sulfone.

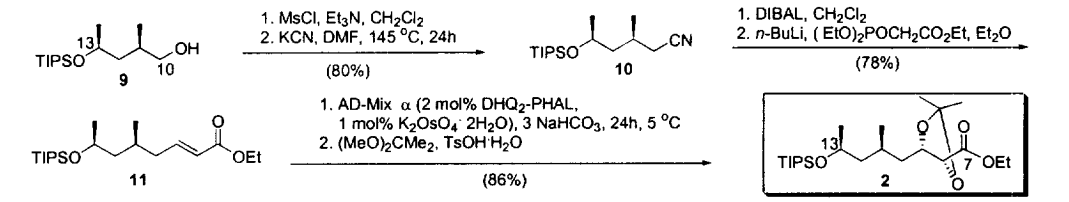
Although we had set out to devise a general synthesis for the common hydrophobic domain, our choice of disconnections was nevertheless influenced by our desire to synthesize ultimately amphidinolide B1. Specifically, we wanted to exploit the homology between the C.10-C.13 hydrophobic domain and the C.22-C.25 hydrophilic domain of this molecule to achieve atom economy. The six carbon "universal" alcohol **9** fulfilled this need (Scheme 3).

Starting from inexpensive (*S*)-ethyl (L)-(+)-lactate, the secondary alcohol was protected as its silyl ether and the ester was converted to iodide **7**. Alkylation with the proline derived tertiary amide **8** followed by reduction with Myers' $LiNH_2BH_3$ gave alcohol **9** as a >5:1 mixture of diastereomers (epimeric at C.11) that was separable by silica gel chromatography only when CH_2Cl_2 was used as the eluent.[14-15] The triisopropyl silyl protecting group proved to be critical in this sequence of reactions. Use of a PMB protected analog of iodide **7** gave predominantly beta-elimination during the alkylation step. Furthermore, the isolated C.11 PMB epimers, even after reduction, could not be separated by chromatography under any conditions.



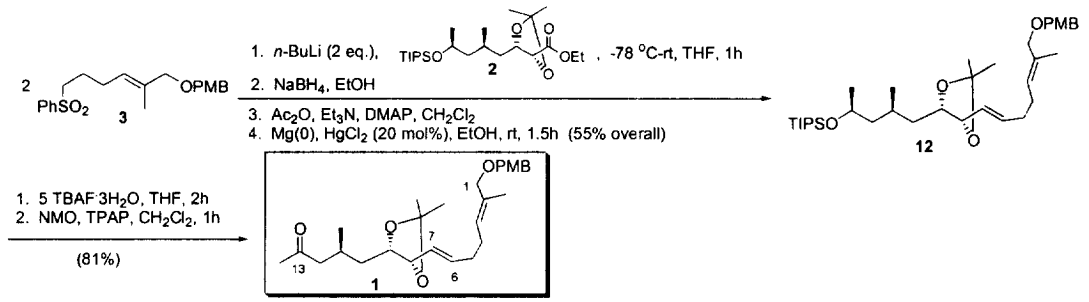
Scheme 3. Synthesis of the universal alcohol.

With the synthesis of alcohol **9** secured, the desired C.7-C.13 ester was prepared in a straightforward manner (Scheme 4). Activation of the alcohol moiety and displacement with KCN gave the one carbon homologated nitrile **10** that was then reduced to the corresponding aldehyde and converted to enoate **11**. The remaining two stereocenters were installed *via* a buffered Sharpless asymmetric dihydroxylation employing fortified AD-mix α.[16] Protection of the diol as the acetonide then set the stage for the Trost/Julia coupling.



Scheme 4. Synthesis of the C.7-C.13 ester.

Addition of 2 eq. of *n*-BuLi to 2 eq. of sulfone **3** in deoxygenated THF (argon, 15 min.) followed by addition of acetonide **2** cleanly gave the keto sulfone in high yield (Scheme 5). Failure to sparge the solvent generally led to low yields and substantial amounts of the butyl ester of acetonide **2**. The diastereomeric mixture of sulfones was then reduced, acylated, and treated with commercial Mg (50-mesh) and 20% Hg to afford the *E*-alkene in >10:1 selectivity and 55% overall yield from ester **2**.[17] We have found that these reducing conditions gave more consistent yields and less deacylation of the intermediate acetoxy sulfones than use of the traditional, but more difficult to prepare, Na/Hg reagent. Deprotection and oxidation of silyl ether **12** gave the desired methyl ketone **1**.[18]



Scheme 5. Synthesis of the hydrophobic domain methyl ketone.

In conclusion, we have completed a practical and convergent synthesis of the conserved C.1-C.13 hydrophobic domain of all seven B-type amphidinolides. A synthesis of the hydrophilic domain specific to amphidinolide B1 and a model coupling of the two domains is presented in the following letter.

References and Notes

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(18) Satisfactory spectroscopic data was obtained for all intermediates. Ketone **1**: ^{1}H NMR (360.1 MHz, $CDCl_3$) δ 7.27 (d, 2H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.6 Hz), 5.79 (d, 1H, J = 15.3 Hz), 5.41 (m, 2H), 4.52 (s, 2H), 3.85 (m, 3H), 3.80 (s, 3H), 3.65 (m, 1H), 2.54 (m, 1H), 2.25 (m, 2H), 2.15 (m, 7H), 1.67 (s, 3H), 1.38 (m, 8H), 0.92 (d, 3H, J = 6.3 Hz). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 208.5, 159.1, 136.1, 132.8, 130.6, 129.3, 127.2, 127.0, 113.7, 108.3, 82.9, 78.8, 75.9, 71.2, 55.2, 51.2, 38.7, 32.2, 30.3, 27.3, 27.2, 27.1, 26.9, 20.2, 14.0. IR (thin film) 2934, 1717, 1614, 1514 cm^{-1}. HRMS (EI) *m/z* 444.2882, $(M)^+$ calcd for $C_{27}H_{40}O_5$: 444.2876. $[\alpha]_D^{20}$ = -2.8 (c = 0.01 g/mL, $CHCl_3$).