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Synthesis of the C(1)–C(25) Fragment of Amphidinol 3: Application of the Double-Allylboration Reaction for Synthesis of 1,5-Diols

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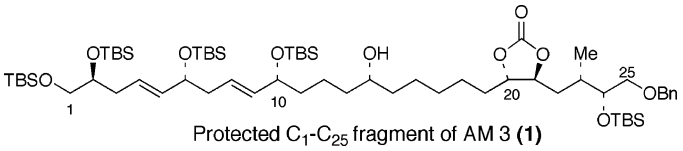
ABSTRACT



Protected C_1-C_{25} fragment of AM 3 **(1)**

A synthesis of the C(1)–C(25) fragment of amphidinol 3 is described. The synthesis features two applications of double allylboration reaction methodology for the highly stereoselective synthesis of 1,5-diol units in the C(1)–C(15) segment.

The amphidinols are a class of polyketide natural products isolated from toxic phytoplanktons contained within the waters surrounding the coasts of Japan.[1−5] These polyhydroxylated marine natural products possess antifungal, hemolytic, cytotoxic, and ichthyotoxic activities.[2,3] Amphidinol 3 (AM 3), isolated in 1996 from cultures of the marine dinoflagellate *Amphidinium klebsii*, is reported to have the greatest antifungal and hemolytic activity of the eight amphidinols isolated to date.[6] AM 3 contains a 67-carbon atom backbone and 25 stereocenters, along with two highly oxygenated tetrahydropyrans and an uncommon structural motif consisting of a series of 1,5-diols within its C2−C15 polyol chain (Scheme 1).[3,7]

The promising biological activity and complex molecular architecture make AM 3 an interesting and challenging target for total synthesis. BouzBouz and Cossy have reported a synthesis of the C(1)−C(14) fragment of AM 3 using enantioselective allylation reactions of aldehydes promoted by a chiral allyltitaium reagent coupled with chemoselective olefin cross-metathesis.[8] We report herein an efficient and convergent synthesis of the C(1)−C(25) fragment of AM 3 utilizing a newly developed method from our laboratory for the synthesis of secondary 1,5-diols.[9]

The C(1)−C(14) fragment of AM 3 contains three stereochemically and structurally distinct 1,5-diol units. The one-pot double allylboration methodology that we introduced in 2002 for the enantio- and diastereoselective synthesis of 1,5-diols seemed to be an ideal method for synthesis of the C(1)−C(14) fragment.[9] Accordingly, we targeted aldehydes **2** and **3** as key intermediates for a fragment coupling sequence via a double allylboration reaction (Scheme 1). Aldehyde **2** also contains a 1,5-diol subunit which can be prepared via a double allylboration reaction.

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(7) For assignment of absolute stereochemistry: Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870.
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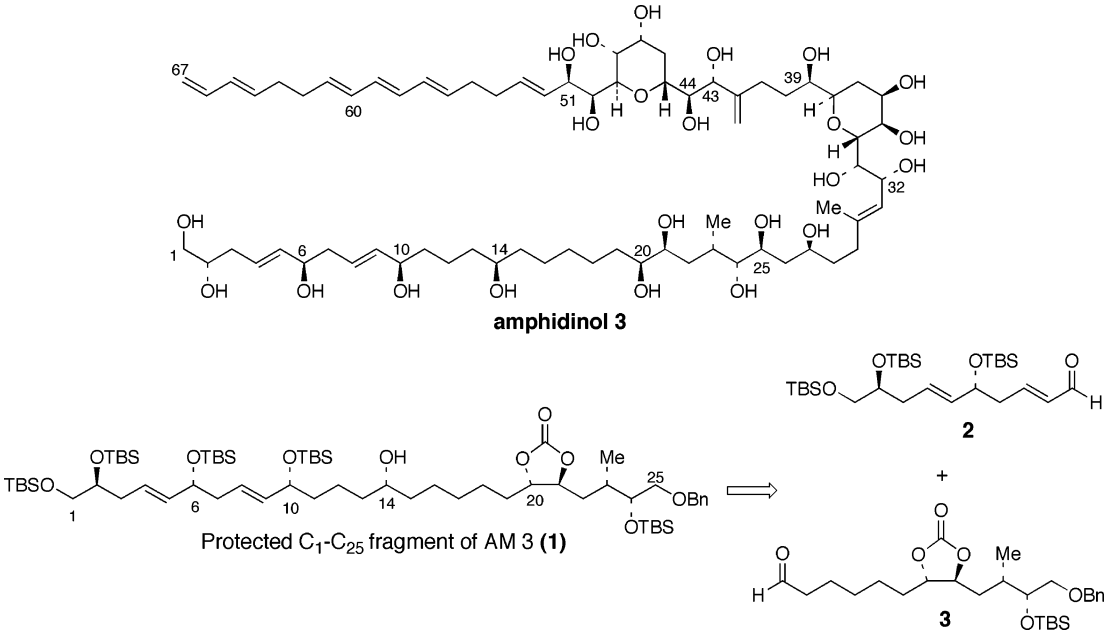
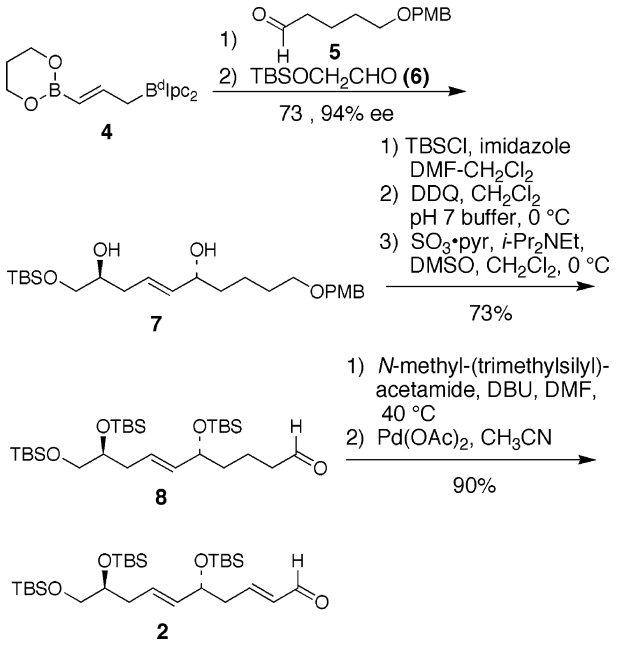
Scheme 1. Amphidinol 3: Retrosynthetic Analysis of the C(1)−C(25) Fragment



The synthesis of **2** commenced with a double allylboration using *in situ* generated **4**,[9] aldehyde **5**,[10] and α-*tert*-butyldimethylsilyloxy acetaldehyde **6.**[11] Thus, addition of 0.5 equiv of **5** to a solution of **4** at −78 °C for 2 h, followed by addition of an excess of **6** with warming to ambient temperature overnight gave (*E*)-1,5-diol **7** in 73% yield and 94% ee (Scheme 2). Protection of diol **7** as the bis-TBS ether, deprotection of the *p*-methoxybenzyl ether, and Parikh−Doering oxidation[12] of the resulting primary alcohol provided aldehyde **8** in 73% yield. Treatment of **8** with *N*-methyl-*N*-(trimethylsilyl)acetamide and catalytic DBU afforded the TMS enol ether[13] which was immediately oxidized with Pd(OAc)$_2$ to give the desired α,*β*-unsaturated aldehyde **2**.[14]

The synthesis of aldehyde **3** began from TBS-protected homoallylic alcohol **9** (Scheme 3).[15] Hydroboration and oxidation of **9**, Parikh−Doering oxidation[12] of the alcohol to the aldehyde, Gilbert−Seyforth homologation to the alkyne,[16,17] and hydrozirconation of the acetylene followed by oxidation of the vinylzirconium intermediate with NBS provided vinyl bromide **10** in 75% combined yield.[18] A Suzuki coupling[19,20] of **10** using Pd(dppf)·CH_2Cl_2, and the alkylborane generated from olefin **11** and 9-BBN provided an inseparable 15:1 mixture of two products in 67% yield. The major product was the desired *trans*-olefin **12**, and the minor product was assigned as the 1,1-disubstituted olefin **13**.[21] Sharpless asymmetric dihydroxylation[22] of this mixture using AD-mix-α and subsequent protection of the resulting diols with triphosgene and pyridine afforded the cyclic

Scheme 2. Synthesis of Aldehyde **2**



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(21) The origin of **13** is unclear, especially since vinyl bromide **10** used in the Suzuki reaction was not contaminated by the 2-bromo regioisomer.
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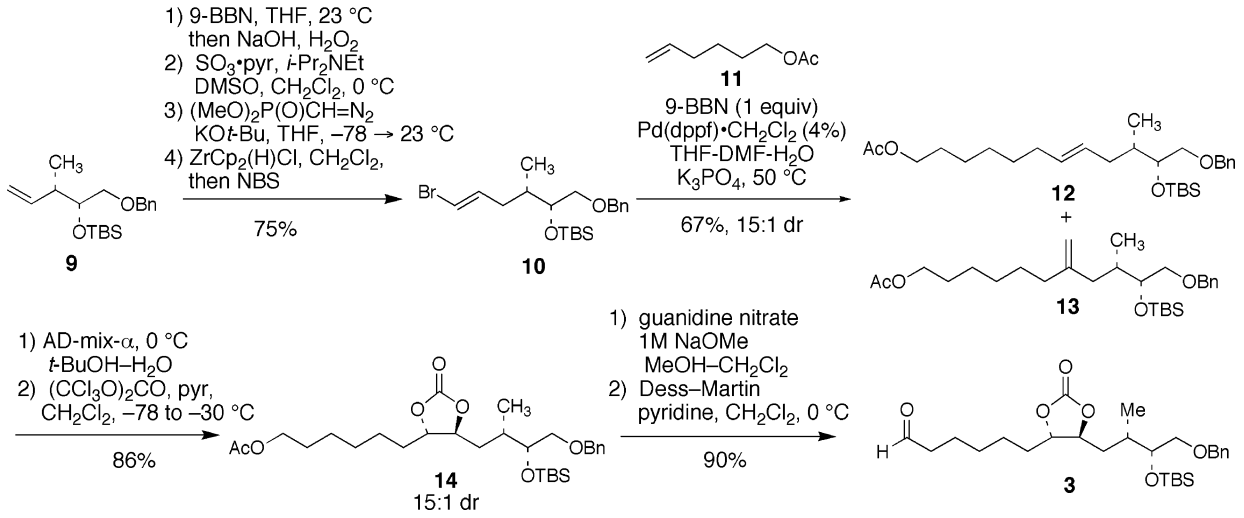
Scheme 3. Synthesis of Aldehyde **3**

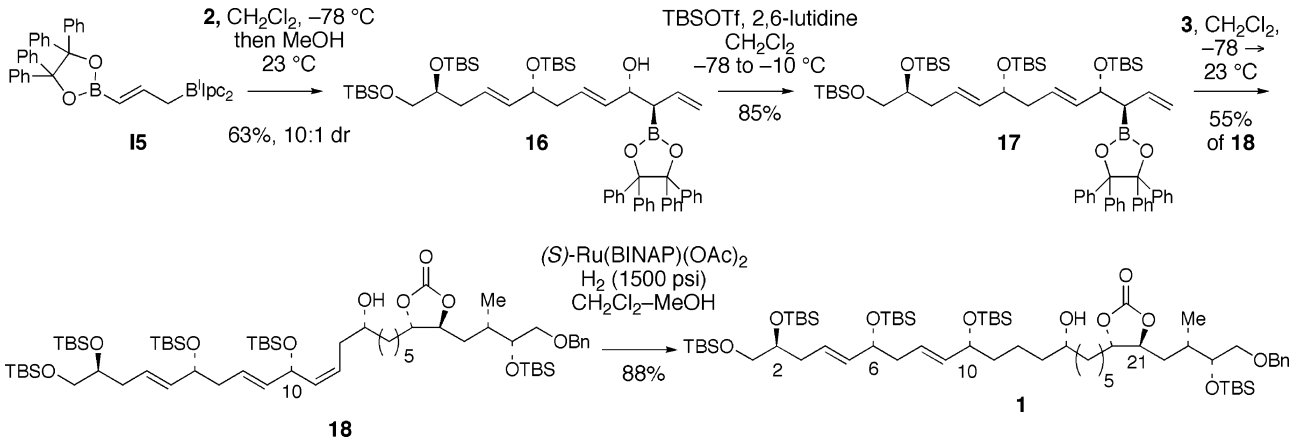


carbonate **14** (in 86% yield from **12**) as a 15:1 mixture of diastereomers. The cyclic carbonates arising from dihydroxylation products of **13** were easily separated by flash chromatography at this stage. Deprotection of the primary acetate in **14** by treatment with guanidine and guanidinium nitrate in MeOH[23] followed by Dess−Martin oxidation[24] yielded aldehyde **3**.

With **2** and **3** in hand, we were ready to perform the fragment assembly double allylboration reaction to complete the synthesis of **1**. Instead of performing this reaction according to the one-pot reaction protocol that we have described previously,[9] the double allylboration of **2** and **3** was carried out in an interrupted three-pot process in order to differentiate the two secondary alcohols that are generated during the double allylboration reaction sequence. Thus, treatment of **2** with *in situ* generated **15**[9] at −78 °C for 1.5 h followed by quenching with MeOH provided the *β*-hydroxy-substituted allylboronate **16** in 63% yield as a 10:1 mixture of diastereomers (Scheme 4). The allylic alcohol so produced was protected using TBSOTf and 2,6-lutidine to afford allylboronate **17** in 85% yield. Subsequent treatment of allylboronate **17** with 2 equiv of aldehyde **3** at 23 °C for 48 h then provided homoallylic alcohol **18** in 55% yield along with a 15% yield of other unidentified materials.

Compound **18** contains all the necessary carbons for elaboration to the C(1)−C(25) fragment **1** of AM 3. All that remained to complete the synthesis of this intermediate was hydrogenation of the C(11,12) olefin. The ability to isolate allylboronate **16** from the allylboration of reagent **15** and aldehyde **2** and to protect the C(10) hydroxyl group of **16** to generate **17** were critical to the overall success of this strategy, since the C(10), C(14)-diol of **18** emerges in fully differentiated form from the final allylboration reaction. This permitted us to contemplate utilizing a hydroxyl-directed hydrogenation reaction to reduce the now unneeded C(11,12) olefin.[25,26] In initial experiments, treatment of **18** with Wilkinson's catalyst, $RhCl(P(C_6H_5)_3)_3$, using conditions reported by Fisher provided a nonselective mixture of olefin reduction products.[27] However, treatment of **18** with Noyori's ruthenium catalyst, (*S*)-Ru(BINAP)$(OAc)_2$,[28,29] in CH_2Cl_2−

Scheme 4. Synthesis of the C(1)−C(25) Fragment of AM 3



MeOH under 1500 psi of H_2 afforded **1**, a protected form of the C(1)−C(25) fragment of AM 3, in 88% yield.

In summary, we have developed a highly stereoselective synthesis of the C(1)−C(25) fragment of AM 3 using our double allylboration methodology in both a one-pot and three-pot sequence. We refer to the latter process as the "interrupted double allylboration sequence". The ability to execute the interrupted double allylboration of **2** and **3** allowed for the key intermediate **18** to be prepared with the C(10) and C(14) alcohols fully differentiated, thereby setting the stage for a highly chemoselective hydroxyl-directed reduction of the C(11,12) olefin. Additional progress on the development of an efficient total synthesis of AM 3 will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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