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Synthesis of the C(43)–C(67) Fragment of Amphidinol 3

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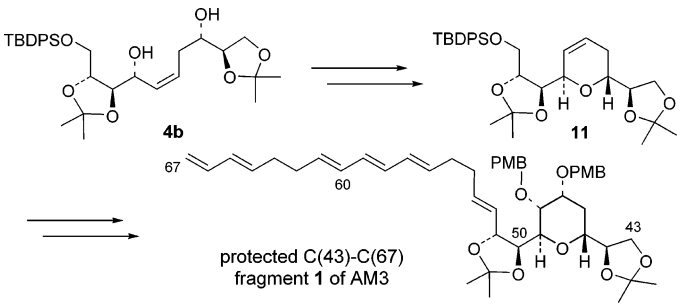
ABSTRACT



A synthesis of the C(43)–C(67) fragment of amphidinol 3 (AM3) has been accomplished by a route that features the use of a double allylboration reaction for synthesis of 1,5-diol 4b, which serves as a precursor to dihydropyran 11.

The amphidinols are a class of natural products isolated from the marine dinoflagelates *Amphidinium* sp. that display antifungal, hemolytic, cytoxic, and ichthyotoxic activities.[1] Of the 13 polyketide metabolites in this family, amphidinol 3 (AM3) is one of the most biologically active, with antifungal activity against *Aspergillus niger* and hemolytic activity on human erythrocytes.[1c] AM3 effects cholesterol-dependent membrane disruption, leading to speculation that its mode of action may, in part, be due to disruption of cell membranes.[1c]

The complex structure of AM3 makes it an interesting synthetic target. It contains a C(52)−C(67) skipped polyene chain, a series of 1,5-diols within the C(2)−C(15) region, two highly substituted tetrahydropyran units, and a total of 25 stereocenters on a contiguous 67 carbon backbone. Since Murata's assignment of the absolute configuration of AM3 appeared in 1999,[2] a number of synthetic studies toward AM3 have been disclosed, including reports from Cossy,[3] Rychnovsky,[4] Paquette,[5] and our laboratory.[6] Herein, we describe a synthesis of the protected C(43)−C(67) fragment **1** of AM3 via the intermediacy of pyran **3**, which will also serve as a precursor to the stereochemically identical C(32)−C(39) tetrahydropyran unit.

Analysis of the C(44)−C(51) and C(32)−C(39) tetrahydropyran units of AM3 reveals these fragments to be identical, suggesting that they should be synthesized from a common intermediate (Figure 1). Disconnection of the C(42)−C(43) and the C(25)−C(26) bonds gives major fragments **1** and **2** (plus the C(1)−C(25) polyol fragment previously synthesized in our group; not shown).[6] Intermediates **1** and **2** can be simplified to the tetrahydropyran **3**, which

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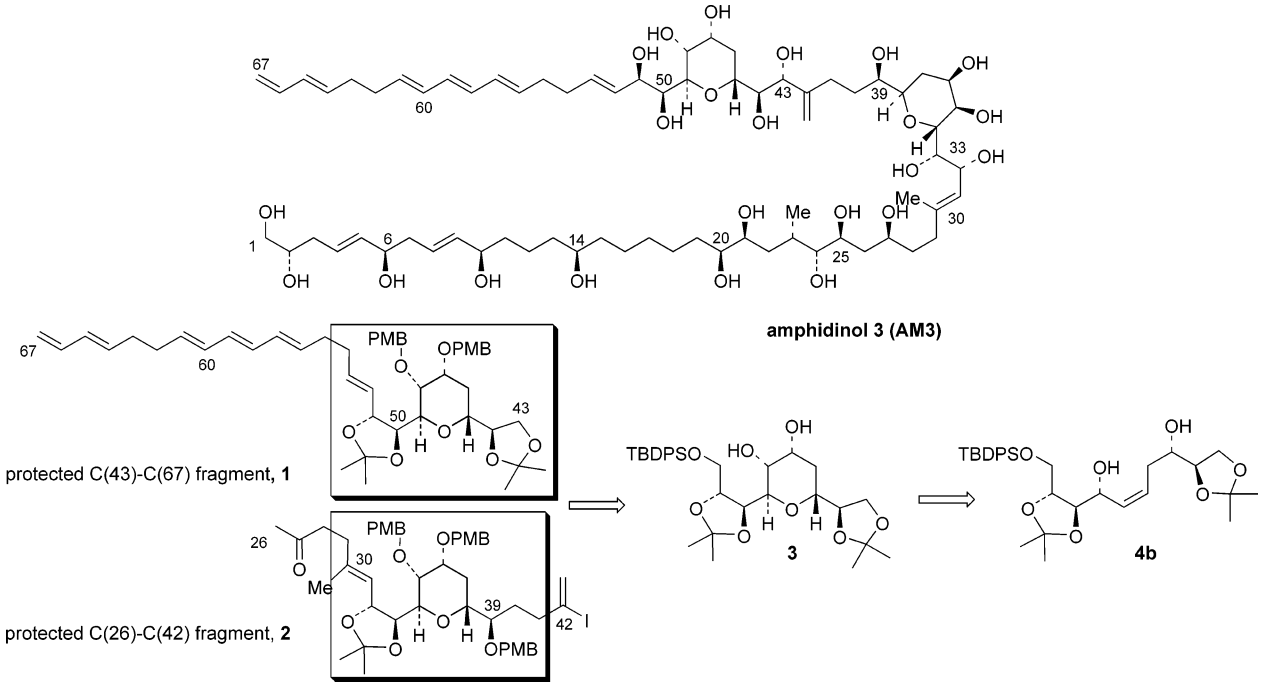
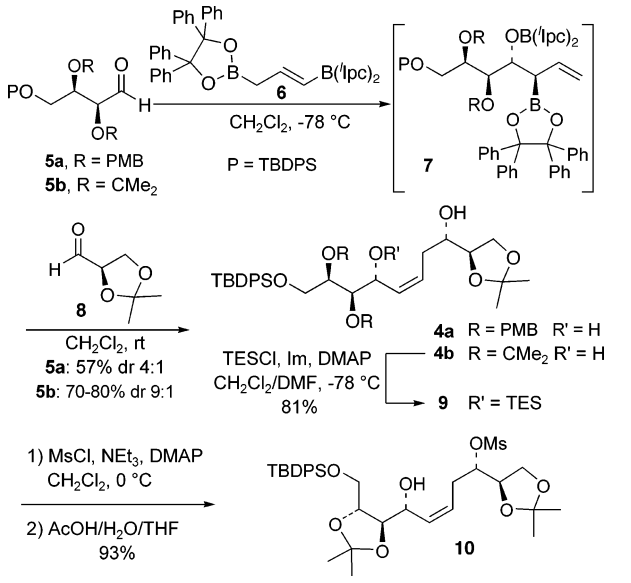


Figure 1. Retrosynthetic analysis.

contains all of the stereocenters present in **1** and **2**. We envisioned that tetrahydropyran **3** could be accessed via dehydrative cyclization[7] of *syn*-1,5-diol **4b**, which in turn would be synthesized by using the double allylboration reaction methodology developed in this laboratory.[8]

Our initial goal was to prepare a differentially functionalized derivative of **4b** that would serve as a precursor to pyran **3**. Accordingly, we targeted an intermediate such as hydroxy mesylate **10** to serve as the immediate precursor of **3** (Scheme 1).[7] In initial studies, in situ generated γ-boryl-substituted allylborane **6**[8] was treated with aldehyde **5a**[9] (0.8 equiv) at −78 °C. After the first allylboration was allowed to proceed to completion at −78 °C, D-glyceraldehyde acetonide[10] was added and the reaction mixture was allowed to warm to ambient temperature overnight. This sequence provided the *syn*-1,5-diol **4a** in 57% yield and 4:1 dr. Investigation of the selectivity of each allylation reaction (by isolating the intermediate allylboronate **7** in Scheme 1) revealed that the initial reaction of aldehyde **5a** and allylborating reagent **6** is stereochemically mismatched.[11] Fortunately, use of acetonide-protected aldehyde **5b**[12] in place of **5a** resulted in significantly improved mismatched double diastereoselectivity in the first allylboration step; ultimately, a 70−80% yield of *syn*-1,5-diol **4b** was obtained with an overall reaction selectivity of 9:1 dr after the second allylboration reaction. Because attempts to accomplish the selective mesylation of **4b** were unsuccessful, we pursued the stepwise functionalization approach that we recently reported.[7] Thus, treatment of **4b** with TESCl (1.05 equiv), imidazole, and DMAP at −78 °C provided the mono-TES ether **9** in 81% yield, with >20:1 regioselectivity for silylation of the allylic alcohol. The homoallylic hydroxyl group was then functionalized as a mesylate and the allylic

Scheme 1. Synthesis of Mesylate **10**



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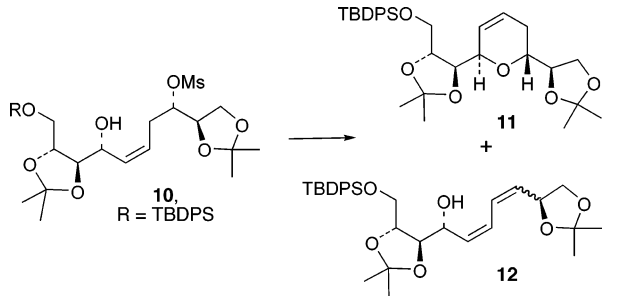
TES group removed under acidic conditions to give cyclization precursor **10** (93% yield from **9**).

With hydroxy mesylate **10** in hand, we turned our attention to the cyclization of **10** to dihydropyran **11**. This transformation was complicated by a competing elimination pathway (Table 1). Initial attempts to effect the cyclization of **11** using

Table 1. Cyclization of Mesylate **10** to Dihydropyran **11**



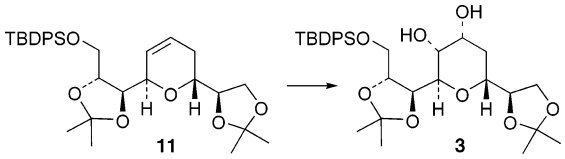
entry	conditions	10/11/12[a]	yield of 11 (%)
1	KHMDS, THF, −78 °C	26:0:74	
2	$(Bu_3Sn)_2O$, benzene; DMF 80 °C	74:0:26	
3	$(Bu_3Sn)_2O$, benzene; NMP 150 °C	30:54:16	36
4	KO*t*Bu, *t*-BuOH; 40 °C (0.05 M)	23:50:27	41
5	KO*t*Bu, *t*-AmOH, 0 °C (0.03 M)	0:85:15	80

[a] Ratio determined by ^{1}H NMR analysis.

a strong base such as KHMDS resulted in exclusive formation of diene **12** (entry 1, Table 1). We anticipated[7] that use of the less basic tributylstannyl ether[13] generated from alcohol **10** would minimize elimination and favor the cyclization to dihydropyran **11**. However, the requisite tributylstannyl ether, prepared by treatment of **10** with $(Bu_3Sn)_2O$ in benzene, was not sufficiently nucleophilic to undergo cyclization at 80 °C. Although the cyclization occurred at higher temperatures (150 °C), significant decomposition was observed and only poor yields of **11** were obtained (entry 3, Table 1). After examining a number of other bases, we discovered that KO-*t*-Bu in protic solvents, under high dilution conditions, gave attractive mixtures (2:1) of **11** relative to the diene **12**. Further optimization of the reaction solvent (*tert*-amyl alcohol), temperature (0 °C), and concentration (0.03 M) provided **11** and **12** with 85:15 selectivity (entry 5, Table 1). Dihydropyran was obtained in 80% isolated yield under these conditions.

We turned next to the dihydroxylation reaction required to set the final stereocenters in tetrahydropyran **3**. Unfortunately, only a slight preference for dihydroxylation on the bottom face of **11** was observed (dr 1.6:1) under standard OsO_4/NMO conditions (entry 1, Table 2).[14] Attempts to improve the facial selectivity, through the use of the Sharpless asymmetric dihydroxylation protocol[15] with the

Table 2. Dihydroxylation of Dihydropyran **11**

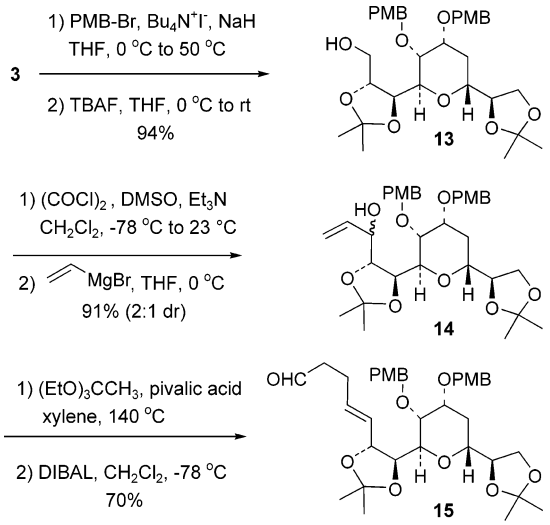


entry	conditions	yield (%)	dr
1	OsO_4, NMO, acetone−H_2O	80	1.6:1
2	$K_2OsO_2(OH)_4$, DHQD-IND, K_3FeCN_6, K_2CO_3, *t*-BuOH−H_2O	97	3:1
3	OsO_4, TMEDA, CH_2Cl_2, −78 °C	75	9:1

DHQD-IND ligand,[16] provided a slight increase in selectivity (dr 3:1). We found, however, that the diastereoselectivity could be further improved through the use of stoichiometric OsO_4 and TMEDA in CH_2Cl_2 −78 °C,[17] which provided tetrahydropyran **3** in 75% yield and with 9:1 diastereoselectivity (entry 3, Table 2).

Synthesis of the C(43)−C(67) polyene fragment was initiated by protection of **3** as the bis-PMB ether followed by deprotection of the TBDPS group, which delivered primary alcohol **13** in 94% yield (Scheme 2). Oxidation of

Scheme 2. Synthesis of Aldehyde **15**



13 using the Swern protocol[18] and treatment of the resulting aldehyde with vinylmagnesium bromide gave allylic alcohol **14** in 91% yield as a 2:1 mixture of diastereomers. Subjection of this mixture to a Johnson ortho ester Claisen rearrangement[19] followed by DIBAL reduction of the resulting ester provided aldehyde **15** in 70% yield.

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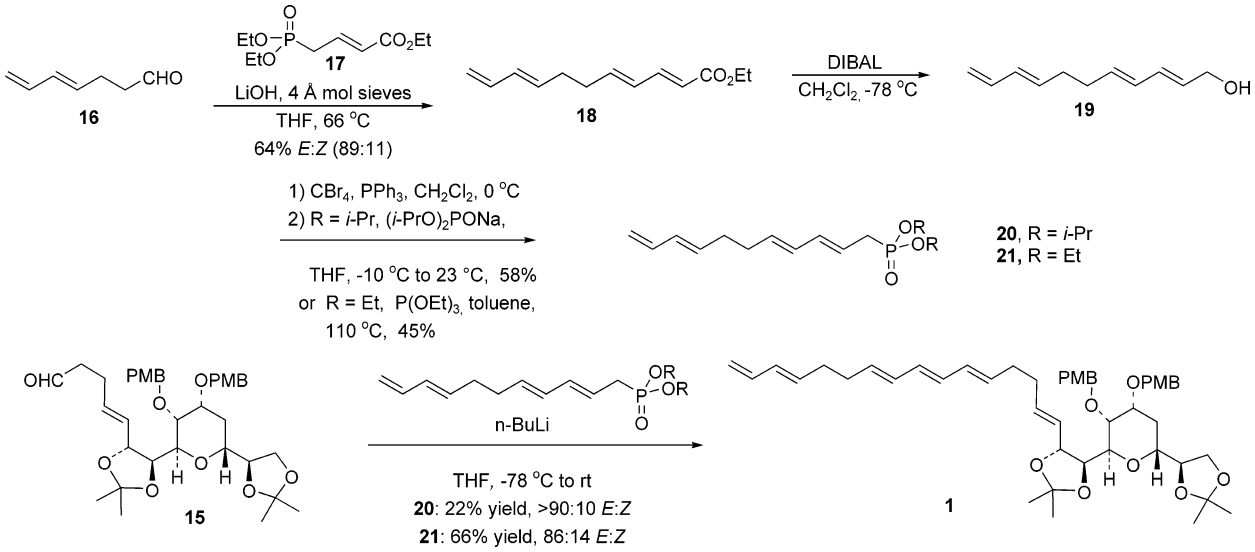
Scheme 3. Synthesis of the C(43)−C(67) Fragment of AM3



Our plan was to subject pyran **15** to a Horner−Wadsworth−Emmons olenfination reaction with dienylic phosphonate **20** or **21** to complete the synthesis of the C(43)−C(67) fragment **1** (Scheme 3). The synthesis of phosphonates **20** and **21** commenced with the homologation of (*E*)-hepta-4,6-dienal (**16**)[20] with commerically available phosphonate **17**, thereby providing tetraene **18**. DIBAL reduction of **18** afforded alcohol **19**, which was converted to the primary bromide upon treatment with CBr_4 and PPh_3. The sensitive dienylic bromide was immediately treated with either sodium diisopropyl phosphite or triethyl phosphite to give **20** and **21**, respectively. Olefination of aldehyde **15** with diisopropyl phosphonate **20** proceeded with 90:10 *E*/*Z* selectivity,[21] albeit in only 22% yield (best under the various conditions examined), owing to oligomerization of the aldehyde **15**. Use of the more reactive diethyl phosphonate **21** led to the isolation of **1** in 66% yield, but with diminished selectivity (86:14 *E*/*Z*).

In summary, we have synthesized the C(43)−C(67) fragment **1** of AM3 via the intermediacy of tetrahydropyran **3**, an intermediate that we plan also to elaborate into the C(26)−C(42) tetrahydropyran fragment **2**. Tetrahydropyran **3** was synthesized in six steps (30% yield) from aldehyde **5b** via a sequence featuring the double-allylboration reaction with **6** and the base-mediated cyclization of hydroxy mesylate **10** to dihydropyran **11**. Further progress on the synthesis of AM3 will be reported in due course.

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Supporting Information Available: Experimental procedures and full 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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