Polyketides

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Synthesis of the C31–C67 Fragment of Amphidinol 3**

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The amphidinols are a structurally unique group of metabolites isolated from the marine dinoflagellates *Amphidinium klebsii* and *Amphidinium carterae*.[1] Amphidinol 3 (AM3; **1**) is one of the most biologically active compounds in this class, as it exhibits potent hemolytic activity against human erythrocytes and antifungal activity against *Aspergillus niger*.[1] Key structural features of AM3 include two highly substituted tetrahydropyran (THP) rings, a long irregular polyol domain, and a skipped polyene chain all distributed over a flexible 67-carbon backbone. The absolute stereochemistry of AM3 was elucidated by Murata and co-workers by using a new and powerful *J*-based NMR spectroscopic technique.[1d,2] Because of its complex molecular architecture and substantial biological activity, AM3 has emerged as an important synthetic target, and a number of recent efforts toward AM3 have been reported.[3] Herein, we disclose the synthesis of the fully protected C31–C67 fragment.

Our approach to AM3 dissects the molecule into three main fragments: polyene **2**, bisTHP core **3**, and the lower polyol fragment (Scheme 1). The union of these segments relies on two sequential olefination reactions. To take advantage of the partial symmetry present in the molecule, both THP rings in the C31–C52 core fragment **3** will be derived from a common intermediate. Synthesis of the C53–C67 polyene fragment **2** will rely on Pd-catalyzed cross-coupling and the Horner–Wadsworth–Emmons reaction to establish the all-*E*-alkene geometries.

Synthesis of core fragment **3** began with known 2,6-*cis*-THP **4** (Scheme 2), which is available in 11 steps from (D)-(−)-diethyl tartrate.[3a] TMSOTf-mediated allylation of the oxocarbenium ion derived from acetoxy ether **4** proceeded in excellent yield and furnished the desired 2,6-*trans*-THP ring as a 10:1 mixture of diastereomers, which were separated by column chromatography. Axial addition predominated, as expected for the addition to a THP oxocarbenium ion.[4] Protection of the diol as the acetonide and subsequent

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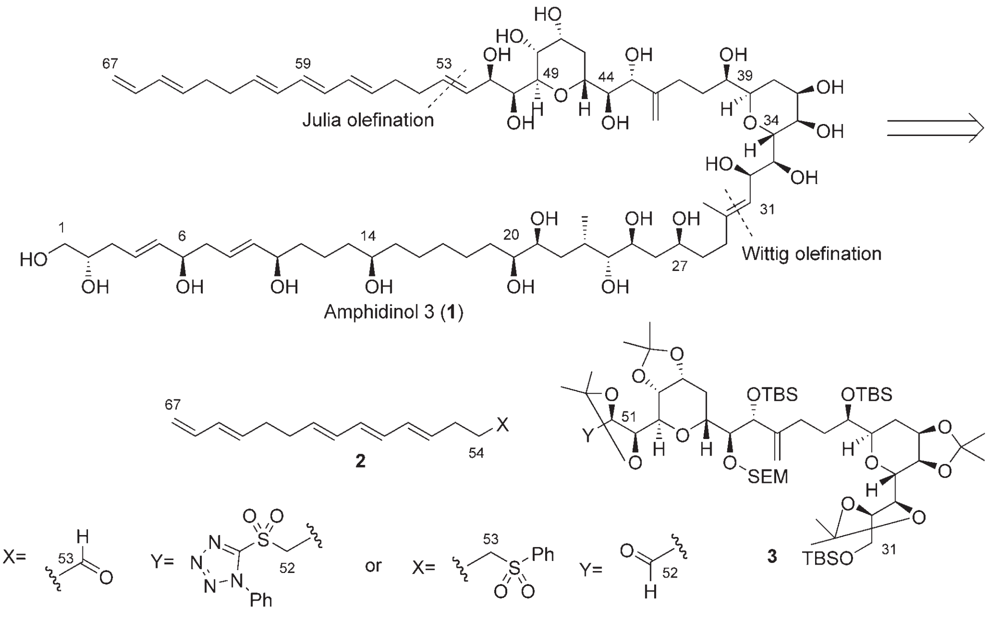
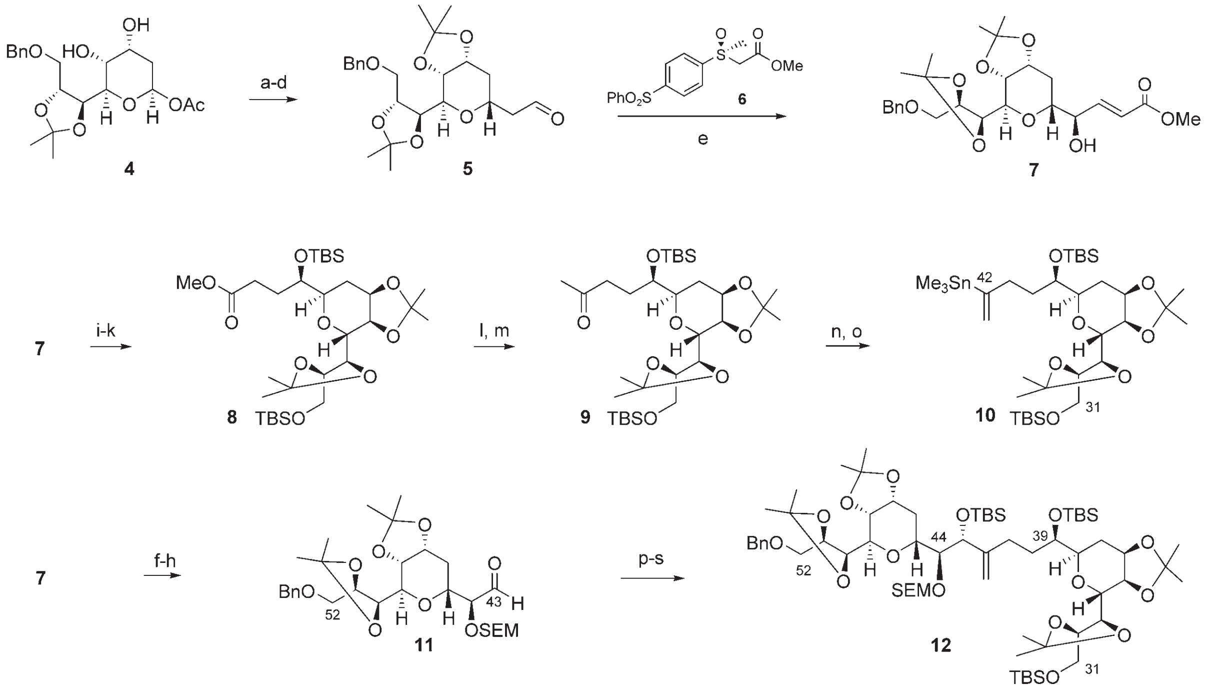


Scheme 1. Retrosynthetic analysis of amphidinol 3 (**1**). TBS = *tert*-butyldimethylsilyl; SEM = β-(trimethylsilyl)ethoxymethyl.



Scheme 2. Synthesis of the C31–C52 fragment **12**. Reagents and conditions: a) allyltrimethylsilane, DTBMP, TMSOTf, CH_2Cl_2, −78 °C; b) K_2CO_3, MeOH (82 % over two steps); c) 2,2-DMP, TsOH, C_6H_6 (82 %); d) 1. O_3, sudan III, CH_2Cl_2; 2. PPh_3, −78 °C→RT (94 %); e) **5**, piperidine, CH_3CN, −5 °C (80 %); f) SEMCl, *i*Pr_2NEt, CH_2Cl_2, 40 °C (85 %); g) OsO_4, NMO, acetone/H_2O (8:1); h) $NaIO_4$, THF/H_2O (1:1; 82 % over two steps); i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT (97 %); j) H_2 (90 psi), Pd/C, THF; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT (84 % over two steps); l) 1. Me(OMe)NH·HCl, *n*BuLi, THF, −78→0 °C; 2. **8**, −78 °C; m) MeMgBr, THF, 0 °C (98 % for two steps); n) 1. LDA, THF, −78 °C; 2. *N*-(5-chloro-2-pyridyl)triflimide, −70 °C (74 %); o) $Me_3SnSnMe_3$, LiCl, $[Pd(PPh_3)_4]$, THF, 80 °C in a sealed tube (85 %); p) 1. **10**, *n*BuLi, THF, −78 °C; 2. **11**; q) Dess–Martin periodinane, pyridine, CH_2Cl_2; r) $Zn(BH_4)_2$, Et_2O, −35 °C (43 % over three steps); s) TBSOTf, 2,6-lutidine, CH_2Cl_2 (73 %). Bn = benzyl, 2,2-DMP = 2,2-dimethoxypropane, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine-*N*-oxide, OTf = trifluoromethanesulfonate, TMS = trimethylsilyl, TsOH = *para*-toluenesulfonic acid.

ozonolysis provided aldehyde **5**. Sulfoxide **6** was prepared as reported[5] and coupled with aldehyde **5** under the hydroxylative Knoevenagel conditions detailed by Trost and Mallart.[6] This crucial [2,3] sulfoxide/sulfenate rearrangement established the last stereogenic center in the THP core of AM3 and furnished allylic alcohol **7** as a 85:15 mixture of diastereomers at C39/C44. The configuration of the major isomer was confirmed by using the advanced Mosher's analysis.[7]

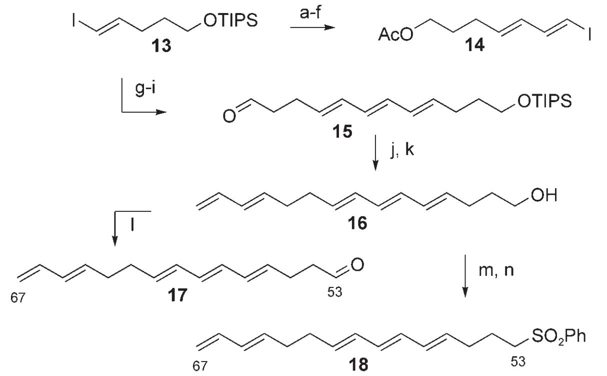
With common intermediate **7** in hand, preparation of both halves of the core section was initiated (Scheme 2). To arrive at the nucleophilic coupling partner **10**, the alcohol **7** was first protected as the TBS ether. A strategic protecting-group exchange was effected by hydrogenolysis of the benzyl group, which was accompanied by reduction of the enoate alkene, followed by silylation of the primary alcohol. The C44 epimers of ester **8**, which arise from the hydroxylative Knoevenagel reaction, were readily separated by column chromatography. Methyl ketone **9** was obtained from ester **8** via the intermediate Weinreb amide.[8] Kinetic deprotonation with LDA followed by trapping with Comins reagent[9] furnished the enol triflate, which was then transformed into vinyl stannane **10** by a Stille cross-coupling with hexamethylditin.[10] Stannane **10** serves as a precursor to a vinyl lithium reagent that will be used to couple the fragments.

With the desired nucleophilic coupling partner in hand, common intermediate **7** was next converted into the requisite aldehyde **11** (Scheme 2). The free alcohol was protected as a SEM ether, and the C39 diastereomers were separated by medium-pressure liquid chromatography (MPLC). Oxidative cleavage of the alkene by using the Johnson–Lemieux protocol afforded aldehyde coupling partner **11**.[11]

Union of the two THP fragments **10** and **11** was accomplished by treatment of stannane **10** with *n*BuLi to afford the nucleophilic vinyl lithium species and subsequent addition to aldehyde **11**. This reaction furnished the C31–C52 bisTHP core of AM3 as a 1:1 mixture of diastereomers. Oxidation of the allylic alcohol mixture with Dess–Martin periodinane[12] followed by chelation-controlled reduction of the resultant ketone with $Zn(BH_4)_2$ afforded the desired *R* alcohol as the sole product. This transformation highlights the selection of the SEM protecting group for the C44 alcohol, which can be removed with other silyl groups, but participates in chelation. The yield over these three steps was 43 %, and the stereochemistry at C43 was verified by using the advanced Mosher's analysis.[7] Protection of the alcohol as the TBS ether afforded the complete, fully protected core fragment **12**.

Synthesis of the C53–C67 skipped polyene is detailed in Scheme 3 and began from *E* vinyl iodide **13**, available after triisopropylsilyl (TIPS) etherification and hydrozirconation/iodinolysis of the corresponding alkynol. Sonagashira cross-coupling[13] of iodide **13** and (trimethylsilyl)acetylene followed by methanolysis of the TMS group furnished the terminal enyne. Selective hydroboration of the alkyne with catecholborane and subsequent iodinolysis afforded the *E*,*E* dienyl iodide with complete geometric selectivity.[14] A simple protecting-group interchange provided iodide **14**.

A Negishi cross-coupling procedure was employed to form the central all-*E* triene.[15] Treatment of another equivalent of vinyl iodide **13** with two equivalents of *t*BuLi followed by transmetallation to zinc furnished the requisite nucleophile. Addition of vinyl iodide **14** in the presence of $[Pd(PPh_3)_4]$ afforded the all-*E* triene with excellent (>20:1) geometric selectivity in 91 % yield. Hydrolysis of the acetate group followed by a Swern oxidation delivered aldehyde **15**.[16]

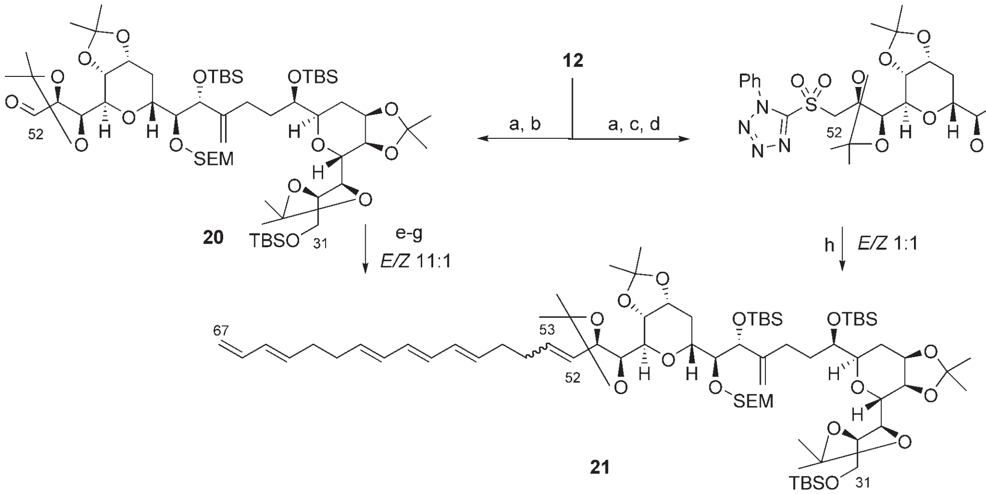


Scheme 3. Synthesis of the C53–C67 fragments **17** and **18**. Reagents and conditions: a) (trimethylsilyl)acetylene, $[Pd(PPh_3)_4]$, pyrrolidine (98 %); b) K_2CO_3, MeOH (99 %); c) 1. catecholborane (74 °C); 2. H_2O; d) 1. NaOH, Et_2O, 0 °C; 2. I_2, 0 °C (70 % over two steps); e) TBAF, THF (100 %); f) Ac_2O, DMAP, pyridine, CH_2Cl_2 (95 %); g) 1. **13**, *t*BuLi, THF, −78 °C; 2. $ZnCl_2$, −78 °C→RT; 3. **14**, $[Pd(PPh_3)_4]$, −20→7 °C (91 %); h) K_2CO_3, MeOH (100 %); i) 1. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; 2. NEt_3, −78 °C→RT (87 %); j) diethylallyl phosphonate, *n*BuLi, HMPA, THF, −78→−10 °C (62 %); k) TBAF, THF (100 %); l) SO_3·pyridine, DMSO, iPr$_2$NEt, CH_2Cl_2 (87 %); m) PPh_3, LiBr, DIAD, THF, 0 °C→RT (ca. 72 %); n) benzenesulfinic acid sodium salt, NaI, $NaHCO_3$, DMF, 45 °C (84 %). DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, HMPA = hexamethylphosphoramide, TBAF = tetrabutylammonium fluoride.

With the all-*E* triene portion of the polyene in place, a semistabilized Horner–Wadsworth–Emmons olefination was utilized to install the terminal *E*-1,3-diene moiety.[17] Treatment of diethylallyl phosphonate with *n*BuLi in the presence of HMPA, followed by addition of trienal **15** led to the formation of the all-*E* pentaene in 62 % yield. Removal of the TIPS ether moiety furnished alcohol **16**. Note that polyene **16** was synthesized with excellent control over the *E*/*Z* geometry of each double bond. We anticipated that undesired alkene isomers would likely be difficult or impossible to separate. Alcohol **16** was further elaborated to aldehyde **17** and sulfone **18** as potential coupling partners with the bisTHP core.

A report from Paquette and Chang, which describes the union of the polyene segment to one of the protected THP rings of the core of AM3, drew our attention.[3e] They described a highly selective Julia–Kocienski olefination using aldehyde **17** and a β-alkoxy sulfone core fragment. We were intrigued by this result because we too had explored this strategy on several model systems, one of which was very similar to the core fragment prepared by Paquette and Chang. This strategy had proved unselective in our hands, and we chose to pursue an alternate route. The disclosure was interesting enough, however, to prompt us to attempt that same coupling on the fully elaborated core.

Further elaboration of bisTHP fragment **12** to the desired sulfone nucleophile began with reductive debenzylation using LiDBB to reveal the primary alcohol (Scheme 4).[18] No reduction of the allylic ether at C43 was observed under the reaction conditions. The phenyltetrazole sulfide was introduced under conditions developed by Mitsunobu,[19] followed



Scheme 4. The union of the polyene and core fragments. Reagents and conditions: a) LiDBB, THF, −78 °C (98 %); b) Dess–Martin periodinane, pyridine, CH_2Cl_2 (100 %); c) PPh_3, phenyltetrazole thiol, DIAD, THF, 0 °C→RT (86 %); d) $[Mo_7O_{24}(NH_4)_6]\cdot 4H_2O$, H_2O_2, EtOH (59 %); e) 1. **18**, LDA, THF, −78 °C; 2. **20**, −78 °C→RT (76 %); f) Bz_2O, DMAP, pyridine, CH_2Cl_2 (89 %); g) Na(Hg), Na_2HPO_4, THF/MeOH (3:1), −20 °C (72 %); h) 1. **19**, KHMDS, THF, −78 °C; 2. **17**, −78 °C→RT (40 %). Bz_2O = benzoic anhydride, KHMDS = potassium bis(trimethylsilyl)amide, LiDBB = lithium di-*tert*-butylbiphenylide.

by molybdate-mediated oxidation[20] to provide sulfone **19**. A suitable electrophile was generated by Parikh–Doering oxidation of alcohol **16**[21] to furnish aldehyde **17** (Scheme 3).

The Julia–Kocienski olefination[22] was carried out by treating a solution of sulfone **19** in THF at −78 °C with KHMDS, followed by addition of aldehyde **17**. In accord with our model studies, the coupling of these two fragments proceeded in an unselective manner to furnish the C31–C67 fragment of AM3 (**21**) in 40 % yield as a 1:1 mixture of *E*/*Z* isomers. These results stand in contrast to those obtained by Paquette and Chang. Subtle differences between substrates, reagents, and even the scale of the reactions may be responsible for these divergent outcomes.

An alternate strategy we explored for uniting the polyene with the core relied on the Julia–Lythgoe olefination.[23] The required sulfone **18** (Scheme 3) was synthesized from alcohol **16** by using the Mitsunobu reaction to provide the primary bromide followed by displacement with the sodium salt of benzenesulfinic acid. The requisite aldehyde **20** was available by Dess–Martin oxidation of the alcohol revealed by debenzylation of core fragment **12** (Scheme 4).

In agreement with our earlier model studies, metalation of sulfone **18** with LDA followed by addition of aldehyde **20** afforded the coupled β-hydroxy sulfone product in 76 % yield (Scheme 4). Acylation of the alcohol with benzoic anhydride followed by elimination with sodium amalgam afforded the C31–C67 section of AM3 (**21**) with a satisfying 11:1 *E*/*Z* ratio. This sequence proceeded in good yield, was very selective, and afforded the product cleanly. In our hands, the Julia–Lythgoe procedure was reproducible and led to fewer byproducts than the Julia–Kocienski strategy for this coupling.

In summary, the fully protected C31–C67 fragment of amphidinol 3 (**21**), the largest portion of this challenging natural product yet to be disclosed, has been synthesized in a very convergent manner. Key features of the synthesis are the use of common intermediate **7** for the construction of both halves of the bisTHP core (**12**), a highly stereoselective polyene synthesis, and the union of those fragments by a stereoselective Julia–Lythgoe olefination. Our efforts in the total synthesis of amphidinol 3 are ongoing.

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