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Synthesis of the C(26)–C(42) and C(43)–C(67) Pyran-Containing Fragments of Amphidinol 3 via a Common Pyran Intermediate

Jacqueline D. Hicks and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458

roush@scripps.edu

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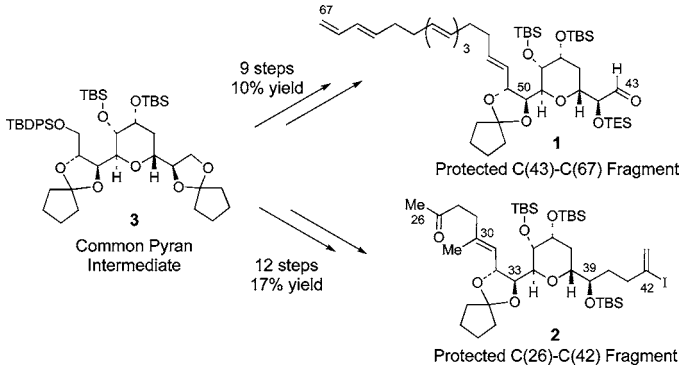
ABSTRACT



The pyran-containing fragments 1 and 2 of AM3 have been synthesized from the common pyran intermediate 3. Careful orchestration of the alcohol protecting groups was necessary to facilitate deprotection of alcohol functionality in the presence of the chemically sensitive polyene chain.

Amphidinol 3 (AM3, Figure 1) is a biologically active polyketide natural product isolated from the marine dinoflagellate *Amphidinium klebsii*.[1] The amphidinols display antifungal activity against *Aspergillus niger* and hemolytic activity of human erythrocytes.[1,2] These biological properties are thought to arise from disruption of cell membranes by the hydrophobic C(52)−C(67) polyene chain of AM3.[1b,2d,3] Other intriguing structural features of the amphidinols include the acyclic polyol region typically containing a series of 1,5-diols and two highly substituted tetrahydropyran ring systems.

The biological activity and structural complexity of AM3 has ignited the interest of several synthetic laboratories,[4] and the Rychnovsky[5] and Paquette[6] groups have assembled large portions of the natural product. We report herein syntheses of the fully functionalized C(26)−C(42) and C(43)−C(67) pyran-containing fragments of AM3.

Our retrosynthetic disconnection of AM3 provides three major fragments (Figure 1): the C(43)−C(67) fragment **1**,

(1) (a) Satake, M.; Murata, M.; Yasumoto, T.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **1991**, *113*, 9859. (b) Paul, G. K.; Matsumori, N.; Konoki, K.; Sasaki, M.; Murata, M.; Tachibana, K. *Harmful and Toxic Algal Blooms. Proceeding of the Seventh International Conference on Toxic Phytoplankton*; Yasumoto, T., Oshima, Y., Fukuyo, Y., Eds.; UNESCO: Sendai, Japan, 1996; p 503.

(2) (a) Paul, G. K.; Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 6279. (b) Paul, G. K.; Matsumori, N.; Konoki, K.; Murata, M.; Tachibana, K. *J. Marine Biotech.* **1997**, *5*, 124. (c) Morsy, N.; Matsuoka, S.; Houdai, T.; Matsumori, N.; Adachi, S.; Murata, M.; Iwashita, T.; Fujita, T. *Tetrahedron* **2005**, *61*, 8606. (d) Morsy, N.; Houdai, T.; Matsuoka, S.; Matsumori, N.; Adachi, S.; Oishi, T.; Murata, M.; Iwashita, T.; Fujita, T. *Bioorg. Med. Chem.* **2006**, *14*, 6548. (e) Echigoya, R.; Rhodes, L.; Oshima, Y.; Satake, M. *Harmful Algae* **2005**, *4*, 383.

(3) (a) Houdai, T.; Matsuoka, S.; Matsumori, N.; Murata, M. *Biochim. Biophys. Acta Biomembranes* **2004**, *1667*, 91. (b) Houdai, T.; Matsuoka, S.; Morsy, N.; Matsumori, N.; Satake, M.; Murata, M. *Tetrahedron* **2005**, *61*, 2795.

(4) (a) Colobert, F.; Kreuzer, T.; Cossy, J.; Reymond, S.; Tsuchiya, T.; Ferrie, L.; Marko, I. E.; Jourdain, P. *Synlett* **2007**, 2351. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451. (c) Dubost, C.; Marko, I. E.; Bryans, J. *Tetrahedron Lett.* **2005**, *46*, 4005.

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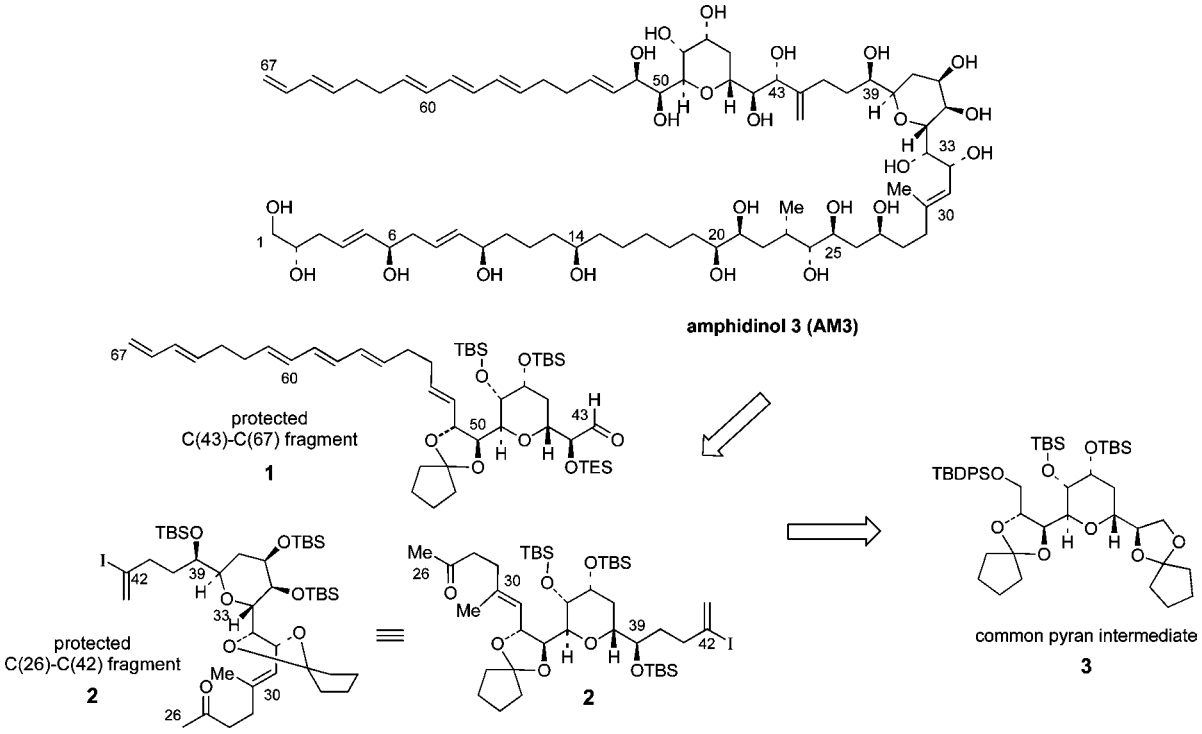


Figure 1. Retrosynthetic analysis of amphidinol 3.

the C(26)−C(42) fragment **2**, and the acyclic polyol fragment (previously synthesized in our laboratory, not shown).[7] We envisioned that the C(42)−C(43) bond between the two pyran-containing fragments would be formed via the coupling of aldehyde **1** and a vinyl metal species formed from iodide **2**. Fragments **1** and **2** can be further simplifed to pyran **3**, an intermediate containing all of the stereocenters within each fragment.

We have previously reported the synthesis of polyene **4**[8] and had planned to elaborate this fragment to an aldehyde similar to **1**. However, attempted deprotection of the terminal C(43,44) acetonide of **4** to progress toward the required C(43) aldehyde could be accomplished only in ≤20% yield (Figure 2), despite examining a number of protic and Lewis acidic conditions that had been effective on intermediates that lack the polyene side chain. Significant decomposition of the polyolefinic intermediates occurred under all the conditions examined.[9] These efforts alerted us to the sensitivity of the polyolefin-containing intermediates and foreshadowed potential problems later in the synthesis were we to continue with acetonide protecting groups for the vicinal diols. The results also prompted us to pilot the removal of the PMB ethers in the presence of the skipped-polyene. However, employing conditions that were effective on earlier intermediates lacking the skipped-polyene unit,[10] we were unable to effect deprotection of **4**—likely due to competing DDQ oxidation of the triene.[11]

The unsuccessful deprotection reactions summarized in Figure 2 prompted us to reexamine our protecting group strategy. After considering several options, we concluded that

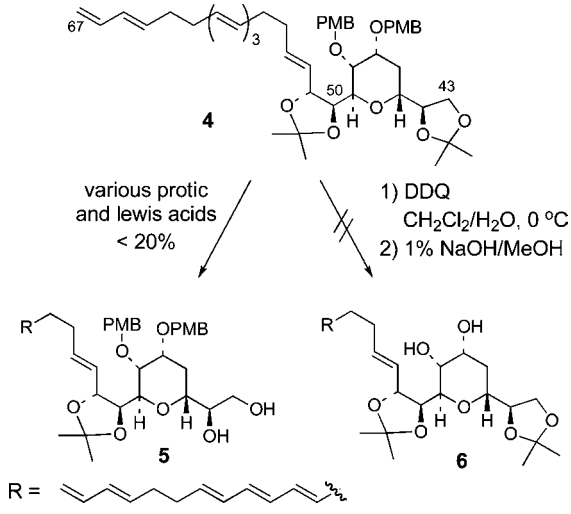


Figure 2. Deprotection studies of polyene **4**.

(5) (a) De Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853. (b) De Vicente, J.; Huckins, J.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7258. (c) Huckins, J. R.; De Vicente, J.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4757.

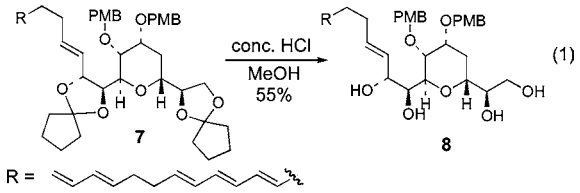
(6) (a) Chang, S.-K.; Paquette, L. A. *Synlett* **2005**, 2915. (b) Paquette, L. A.; Chang, S.-K. *Org. Lett.* **2005**, *7*, 3111. (c) Bedore, M. W.; Chang, S.-K.; Paquette, L. A. *Org. Lett.* **2007**, *9*, 513.

(7) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411.

(8) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509.

(9) A table containing conditions examined can be found in the Supporting Information.

cyclopentylidene ketals might be a good replacement for the acetonide protecting groups of **4**. Cyclopentylidene ketals are more acid labile than acetonides,[12] and the use of cyclic ketals would result in minimal changes to our previously developed route.[8] To test this proposal, we performed some initial experiments with polyene **7** (eq 1).[13] These studies revealed that the terminal C(43,44) cyclopentylidene ketal and the more acid stable C(50,51) *trans*-cyclopentylidene ketal could be removed by brief treatment with acidic methanol in modest yield (unoptimized). Encouraged by this result, we chose to explore pyran **3** (Scheme 1) as our common pyran intermediate in order to facilitate late-stage deprotection.

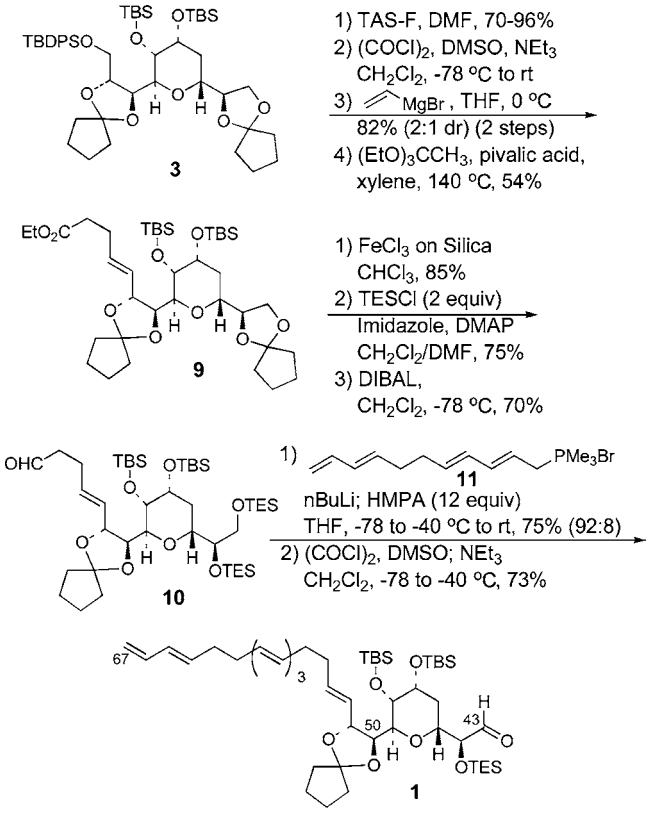


(1)

Accordingly, by using appropriate modifications of our previously reported sequence,[8] we developed a synthesis of the key common pyran intermediate **3** by replacing the problematic acetonide protecting groups in **4** with more acid labile cyclopentylidene ketals. Moreover, the polyene-incompatible PMB ethers of **4** were replaced with TBS ether protecting groups in **3** (see the Supporting Information for details).

The fully functionalized C(43)−C(67) fragment **1** was synthesized from pyran **3** (Scheme 1). Removal of the primary TBDPS ether of **3**, in the presence of the two secondary TBS ethers, by using TAS-F proceeded in 70−96% yield.[14] Swern oxidation of the primary alcohol, addition of vinyl-MgBr to the resulting aldehyde, and then Johnson orthoester Claisen rearrangement[15] of the derived allylic alcohol provided ester **9** with excellent *E*:*Z* selectivity (43% overall yield). We opted to remove the terminal C(43,44) cyclopentylidene ketal of **9** by using $FeCl_3$ on silica gel.[16] We found these conditions to be the most efficent way to selectivity deprotect the terminal acetonide in the presence of the two TBS ethers

Scheme 1. Synthesis of the C(43)−C(67) Fragment



and the internal *trans*-cyclopentylidene ketal; however, the polyene was not stable to these conditions, therefore necessitating deprotection prior to installation of the polyene. Thus, the diol resulting from deprotection of **9** was protected as the bis-silyl ether by using TESCl, and the C(56)-ethoxycarbonyl group was reduced with DIBAL at −78 °C to provide aldehyde **10**. Olefination of **10** with the ylide derived from dimethylphosphonium salt **11** installed the polyene chain in 75% yield and 92:8 *E*/*Z* selectivity. This olefination represents an improvement over our previously published Horner−Wadsworth−Emmons olenfination that we used for the synthesis of **4** (86:14 *E*/*Z*).[8] Swern oxidation of the primary TES ether[17] then provided aldehyde **1**, the fully elaborated C(43)−C(67) fragment of AM3.

Construction of the C(26)−C(42) pyran fragment began by deprotection of the terminal cyclopentylidene ketal of **3** ($FeCl_3$ on silica gel, 85%)[16] to reveal diol **12**, which was converted to epoxide **13** by using Martinelli's selective tosylation protocol (Scheme 2).[18] Treatment of **13** with dilithiopropyne[19] installed the propargyl unit of **14** (85%). Use of the unusual dilithiopropyne reagent was necessary because treatment of **13** with the corresponding Grignard reagent[20] resulted in significant bromohydrin formation.

(10) It is speculated that the two-step deprotection sequence was necessary because after removal of the first PMB ether, oxidation of the second PMB ether results in *p*-methoxybenzylidene acetal formation. The acetal is further oxidized to the benzoate, which then undergoes hydrolysis with basic methanol.

(11) For examples of low-yielding PMB deprotection on polyolefinic substrates see: (a) Couladouros, E. A.; Bouzas, E. A.; Mangos, A. D. *Tetrahedron* **2006**, *62*, 5272. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* **1992**, *57*, 1964. (c) Asato, A. E.; Kiefer, E. F. *Chem. Commun.* **1968**, 1684.

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(13) See the Supporting Information for the synthesis of **7**.

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(15) Johnson, W. S.; Werthermann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(16) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404.

(17) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161.

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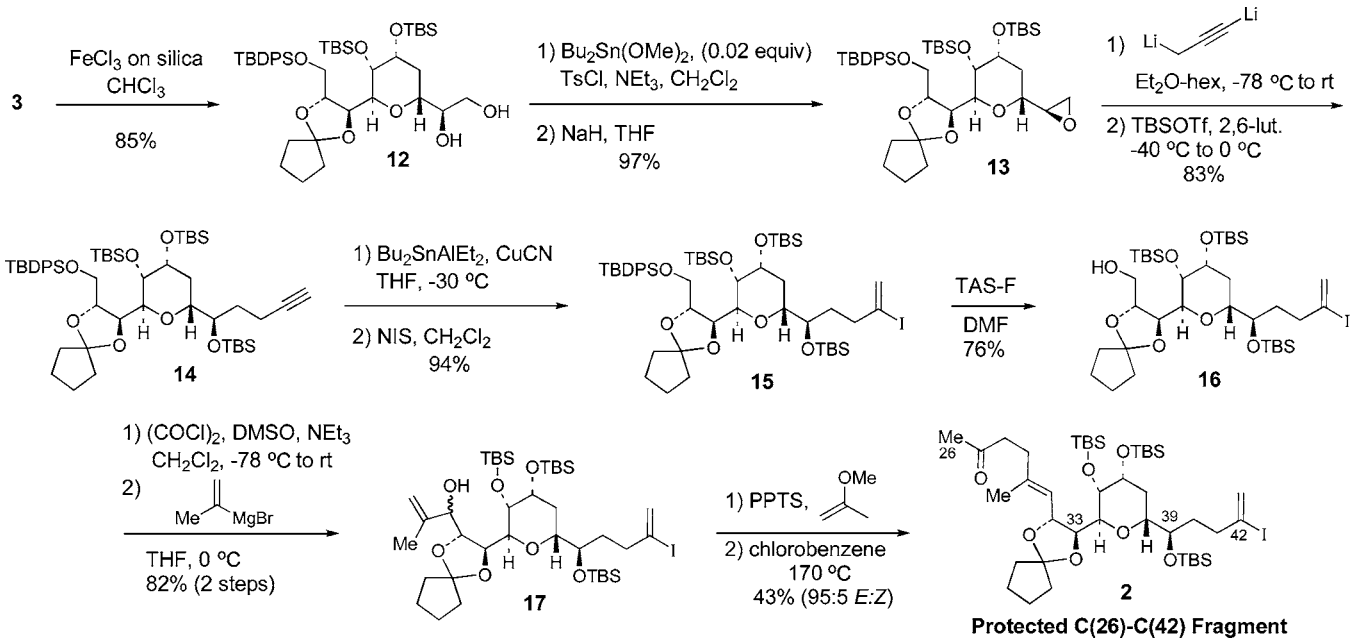
(19) Pereira, A. R.; Cabezas, J. A. *J. Org. Chem.* **2005**, *70*, 2594.

Scheme 2. Synthesis of the C(26)−C(42) Fragment



Protection of the secondary hydroxyl group of the bishomopropargyl alcohol afforded TBS-ether **14** (83% overall from **13**). Stannylalumination[21] of **14** followed by iodination yielded **15** (94%). Deprotection of the primary TBDPS ether using TAS-F[14] provided alcohol **16** (76%), which underwent Swern oxidation and propenyl Grignard addition to afford allylic alcohol **17** as an inconsequential 2:1 diastereomeric mixture (82%). Treatment of **17** with 2-methoxypropane and PPTS generated an intermediate vinyl ether which was heated at 170 °C in chlorobenzene to effect Claisen rearrangement.[22] This provided the C(26)−C(42) pyran fragment **2** with 95:5 *E*/*Z* selectivity in 43% yield. While the efficency of this Claisen sequence is moderate, the yield of **2** from **17** is higher from this two-step sequence than from other Claisen sequences that we explored (e.g., Johnson ortho ester Claisen rearrangement followed by conversion of the methoxycarbonyl to the methyl ketone unit in **2**, 30% yield).

In summary, the fully functionalized pyran-containing fragments **1** and **2** of AM3 have been synthesized from the common pyran intermediate **3**. A revised protecting group strategy was employed to facilitate deprotection of alcohol functionality in the presence of the sensitive polyene chain. The silyl ether and cyclopentylidene ketal protected pyran **3** was elaborated to the C(43)−C(67) fragment in nine steps (10% yield) and to the C(26)−C(42) fragment in 12 steps (17% yield). Further progress toward completion of the total synthesis of amphidinol 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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