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Syntheses of the C1−C14 and C15−C25 Fragments of Amphidinolide C

Dimao Wu and Craig J. Forsyth*

Department of Chemistry and Biochemistry, The Ohio State University, Columbus, Ohio 43210, United States

forsyth@chemistry.ohio-state.edu

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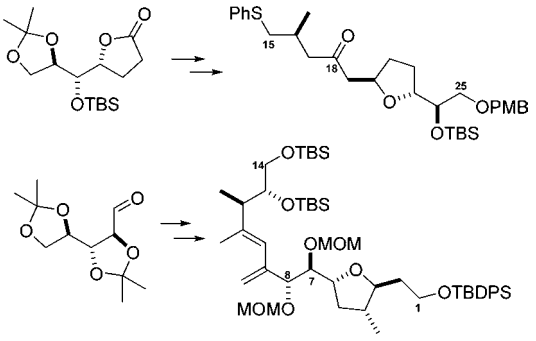
ABSTRACT



Divergent syntheses of the C1−C14 and C15−C25 fragments of amphidinolide C have been achieved. The synthesis of the C15−C25 fragment featured cobalt-catalyzed modified Mukaiyama aerobic alkenol cyclization and sulfur-directed regiocontrolled Wacker oxidation of an internal alkene. The C1−C14 fragment was established by alkenyllithium addition to an aldehyde followed by a challenging olefination of a highly inert C9 ketone.

The amphidinolides represent a large family of marine natural products with 34 structurally varied members. They have been isolated from symbiotic dinoflagellates *Amphidinium sp.* associated with the Okinawan aceol flatworm *Amphiscolops sp.*[1] Among them, the amphidinolide C subgroup including amphidinolide C (**1**, from Y-5, Y-56 and Y71 strain), C2 (**2**, from Y71 strain), C3 (**3**, from Y56 strain), and F (**4**, from Y56 strain) share an identical 25-membered macrolide moiety with different aliphatic polyene substructures attached (Figure 1).[2] Intriguingly, their antitumor activities were highly related to the tail polyene domain, especially the C29 oxidation state. Bearing a free C29−OH, amphidinolide C (**1**) was the only subgroup member displaying remarkable *in vivo* cytotoxicity with IC_{50}'s below 10 ng/mL. Since the stereochemistry of **1** was fully elucidated in 2001−2003,[3] significant synthetic efforts have been made toward amphidinolide C and related macrolides, including a recently reported total synthesis of amphidinolide F.[4] Herein we report synthetic progress toward **1**, focusing on the syntheses of the C1−C14 and C15−C25 fragments.

To facilitate the generation of analogues to support structure−activity relationship studies, a late-stage installation of the C26−C34 polyene domain after establishing the C1−C25 macrolide was planned (Figure 1). Retrosynthetically, the macrolide was disconnected at the C1

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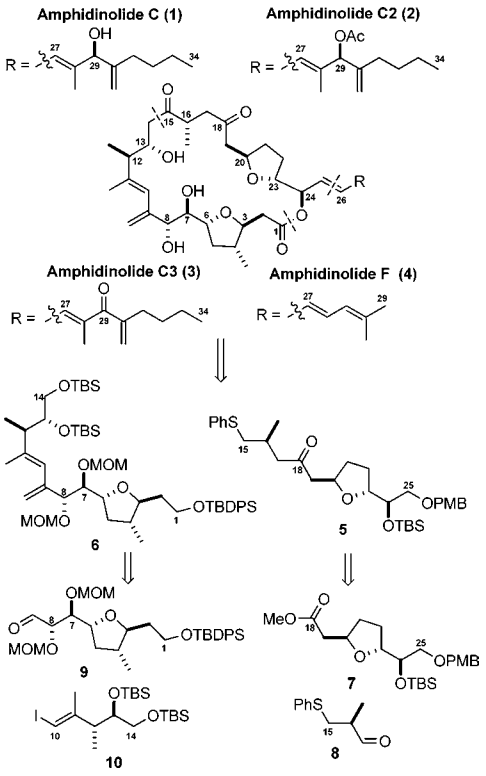
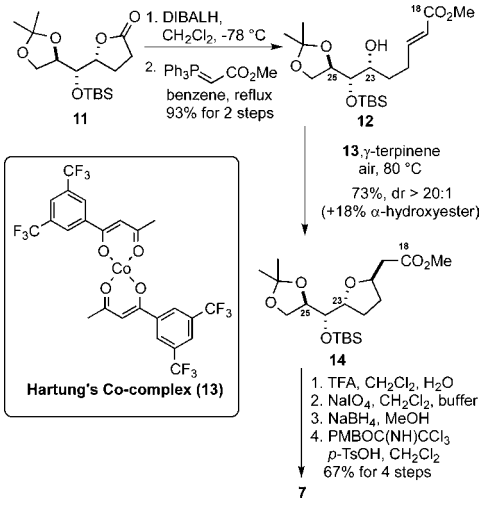


Figure 1. Amphidinolide C subgroup and retrosynthesis.

Scheme 1. Synthesis of Ester **7**



ester and the C14–C15 alkene, with a Yamaguchi macrolactonization[5] and sulfone alkylation[6] envisioned to accomplish these junctions. A similar strategy was used in Carter's total synthesis of amphidinolide F (**4**).[4d] Ketone **5** and diene **6**, containing *trans*-tetrahydrofuran moieties, would be assembled from the corresponding building blocks (**7**/**8** and **9**/**10**, respectively).

The synthesis began with recognizing that the stereochemistry at C23–C24 of **5** could be derived from the known lactone **11** (Scheme 1). Lactone **11** could be prepared via either a vinylogous Mukaiyama aldol process[7] or from carbohydrate precursors.[8] Lactone **11** was subjected to a DIBALH reduction/Wittig reaction sequence[4b] to afford α,*β*-conjugated ester **12**. A variety of heteroconjugate addition conditions were initially surveyed to close the THF ring via intramolecular alkoxide additions upon the acrylate moiety. These included the use of bases KHMDS, NaH, MeONa, *t*-BuOK, DBU, and TBAF, among others. However, the diastereoselectivity of *trans*- vs *cis*-THF ring formation was no more than 2:1, respectively, and the separation of diastereomers was tedious. In contrast, a Mukaiyama aerobic alkenol cyclization catalyzed by Hartung's cobalt complex **13**[9] was applied to **12** to establish the C20–C23 *trans*-THF moiety of ester **14** in good yield and excellent diastereoselectivity. An inherent *trans*-selectivity in this type of cobalt catalyzed Mukaiyama THF ring formation is well established[9] and has been applied in similar contexts, most notably by Pagenkopf.[4h] Although Hartung and co-workers observed complete suppression of overoxidation side products in the presence of *γ*-terpinene at high concentration,[9a] an epimeric mixture of α-hydroxyester side products was unavoidably generated in the reaction mixture here. A few transformations converted the 1,2-acetonide into PMB ether **7** (Scheme 1).

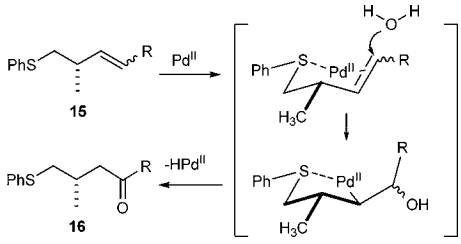


Figure 2. Sulfur-directed regioselective Wacker oxidation.

We envisioned that the C18 ketone within the challenging 1,4-diketone moiety of amphidinolide C might be installed via Raghavan's sulfur-directed regioselective Wacker oxidation of an internal alkene (Figure 2).[10] Presumably, the sulfide moiety would direct palladium to

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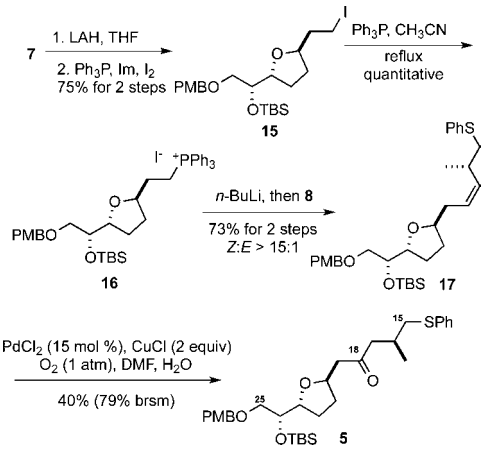
the proximal terminus of the tethered alkene, while water would preferably attack the distal carbon, affording the δ-keto-sulfide regioselectively after reductive elimination. Raghavan's Wacker process was reportedly most efficient with (*E*)-olefins, so this was targeted first.

Surprisingly, Julia-type olefination[11] employing sulfone derivatives of **7** were unreliable in providing the C17−C18 (*E*)-alkene. Alternatively, the anion of phosphonium iodide **16**, prepared from **7** via iodide **15**, was coupled with the known aldehyde **8**[12] under standard (*Z*)-selective Wittig olefination conditions to give alkene **17** in good yield (Scheme 2). Thereafter, an optimized procedure for Raghavan's Wacker oxidation was applied to convert **17** into ketone **5** with moderate yield and excellent regioselectivity, accompanied mostly by untransformed **17**. The (*Z*)-olefin geometry and the enhanced electron donation of sulfides versus sulfoxides may contribute to the observed low catalyst turnover. The C15−C25 fragment **5** was achieved in 12 steps and 13% overall yield in the longest linear sequence from known lactone **11**. Notably, this involved application of Hartung's cobalt-mediated oxacyclization and a sulfur-directed Wacker oxidation.

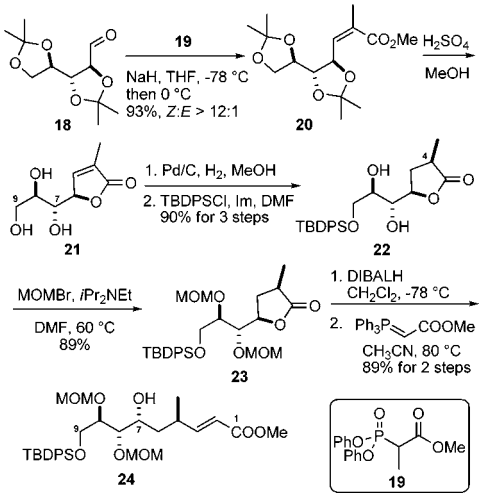
The synthesis of the C1−C9 segment **9** evolved from Roush's route which featured acidic butenolide formation followed by diastereoselective hydrogenation and intramolecular oxo-Michael cyclization (Scheme 3).[4b] Alternatively, we relied upon the known aldehyde **18**[13] arising from δ-gluconolactone as the origin of the C7−C8 stereochemistry instead of Roush allylation to construct the *anti*-stereochemistry at C7−C8. Also, a practical Ando olefination[14] involving diphenyl phosphonate **19** was employed to establish the C4−C5 (*Z*)-alkene. Acidic lactonization with a modified workup[15] afforded triol **21**. Facial selective hydrogenation then established the C4 stereogenic center.[4b] Selective monosilylation and bis-MOM installation provided lactone **23**. Conversion into the corresponding lactol with DIBALH allowed incorporation of the α,β-conjugated ester of **24**.

Intermediate **24** was cyclized to the C3−C6 *trans*-THF ring upon treatment with TBAF,[3,4b] with concomitant loss of the C9 *O*-silyl group (Scheme 4). The C9 alcohol was temporarily resilylated before the C1 ester was reduced, and the resultant alcohol was protected with a robust TBDPS group. Chemoselective cleavage of the C9 *O*-TES ether in the presence of MOM and TBDPS protecting groups was then achieved with PPTS in MeOH/CH_2Cl_2 to give primary alcohol **26**. Parikh−Doering oxidation[16] converted **26** into aldehyde **9** as a prelude to installation of the C10−C14 side chain. For this, we relied upon lithium−halogen exchange of Carter's iodide **10**[4c]

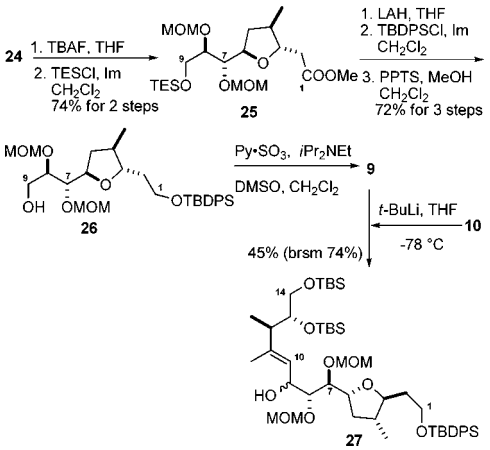
Scheme 2. Synthesis of C15−C25 Fragment **5**



Scheme 3. Preparation of Ester **24**



Scheme 4. Synthesis of Allylic Alcohol **27**



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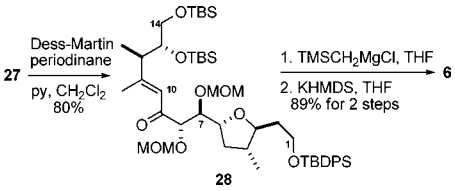
and addition to **9** to provide allylic alcohol **27** as a 1:1 diastereomeric mixture.

In the conversion of **27** into enone **28**, the use of pyridine with Dess-Martin periodinane[17] was superior to sodium bicarbonate powder for buffering acidic species and suppressing decomposition (Scheme 5). As similarly observed by Carter,[4c] methylenation of the C9 ketone was challenging. Several common methylenation reagents failed to convert ketone **28** into the desired diene **6**, including Petasis' reagent,[18] which was effective for Carter's enone. Encouragingly, Takai–Utimoto olefination involving bis(iodozincio)methane and $TiCl_4$[19] provided diene **6** in 40–60% yield. However, the modest and variable yields associated with partial loss of a MOM group and other side products due to the strong Lewis acidity were overall unsatisfactory. Alternatively, Peterson olefination in a two-step protocol[20] provided **6** in reproducibly high efficiency. Specifically, the use of KHMDS rather than *t*-BuOK or KH was the most effective and convenient reagent to initiate the Peterson elimination under basic conditions. The C1–C14 fragment **6** was synthesized from known aldehyde **18** in 11% overall yield in 17 steps in the longest linear sequence.

In summary, the C15–C25 fragment of amphidinolide C was prepared using a Mukaiyama aerobic alkenol cyclization to close the C20–C23 *trans*-tetrahydrofuran moiety and a sulfur-directed regiocontrolled Wacker oxidation to install the C18 ketone. The complementary C1–C14 fragment synthesis featured the assembly of the C3–C6 *trans*-tetrahydrofuran ring by an established intramolecular oxo-Michael cyclization, and an efficient Peterson olefination of the recalcitrant C9 ketone. This work establishes an avenue toward a projected total synthesis of amphidinolide C and targeted analogs.

Scheme 5. Completion of C1–C14 Fragment Diene **6**



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Supporting Information Available. Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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