

Synthesis of the C(18)–C(34) Fragment
of Amphidinolide C and the C(18)–C(29)
Fragment of Amphidinolide F

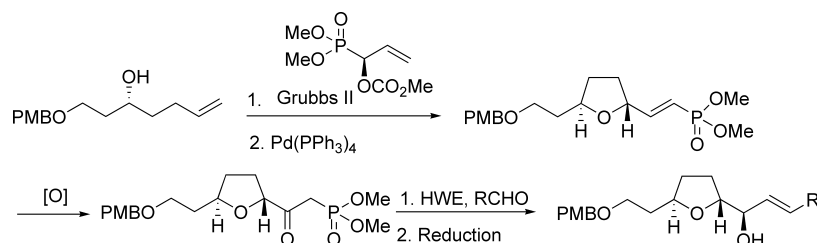
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Received September 28, 2010

ABSTRACT



A convergent synthesis of the C(18)–C(34) fragment of amphidinolide C and the C(18)–C(29) fragment of amphidinolide F is reported. The approach involves the synthesis of the common intermediate tetrahydrofuran- β -ketophosphonate via cross metathesis, Pd(0)-catalyzed cyclization, and hydroboration–oxidation. The β -ketophosphonate was coupled to three side chain aldehydes using a Horner–Wadsworth–Emmons (HWE) olefination reaction to give dienones, which were reduced with L-selectride to give the fragments of amphidinolide C and F.

The amphidinolides are a structurally diverse group of natural products isolated from symbiotic marine dinoflagellates *Amphidinium* sp., found in Okinawan aceol flatworms. Several members of the amphidinolide family possess high levels of cytotoxicity against various cancer cell lines.¹

Amphidinolide C (**1**) (Scheme 1), isolated from the three strains (Y-56, Y-62, and Y-71) of the genus *Amphidinium*, is one of the most cytotoxic members of the amphidinolide family.² Amphidinolide C exhibits cytotoxicity against murine lymphoma L1210 (IC₅₀ 0.0058 μ g/mL) and human epidermoid carcinoma KB (IC₅₀ 0.0046 μ g/mL) in vitro. Interestingly, amphidinolide C2 (**2**) and F (**3**), which vary only in the structure and length of the side chain, are approximately 1000-fold less active, suggesting a crucial role

played by the side chain C(26)–C(34) in determining the biological activity of these molecules.

The unique structural features and potent cytotoxicity render amphidinolide C (**1**), C2 (**2**), and F (**3**) very attractive and challenging targets for total synthesis. The syntheses of several fragments of these molecules have been reported, but they have yet to succumb to total synthesis.³

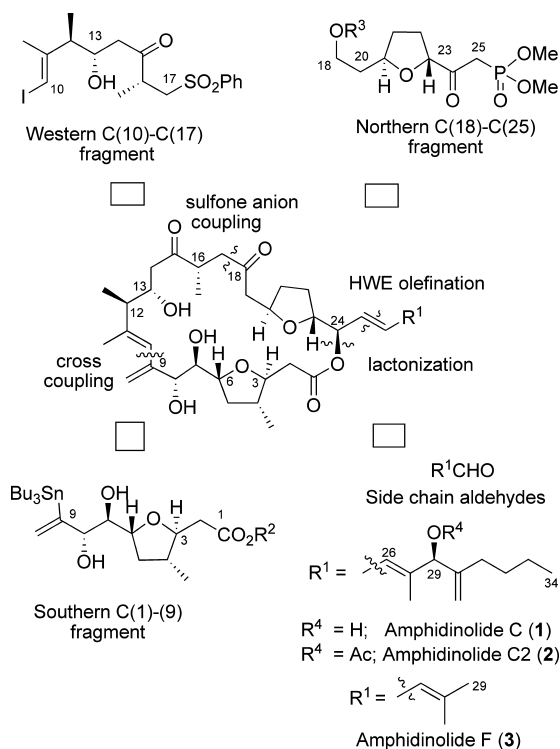
In our retrosynthetic analysis (Scheme 1), amphidinolides C, C2, and F (**1–3**) are dissected into four fragments: the northern C(18)–(25), the southern C(1)–C(9), and the western C(10)–C(17) fragments and the side chains of amphidinolide C, C(26)–(34), and amphidinolide F, C(26)–(29). We have recently reported the synthesis of the C(1)–C(9)

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Scheme 1. Retrosynthetic Analysis of Amphidinolide C

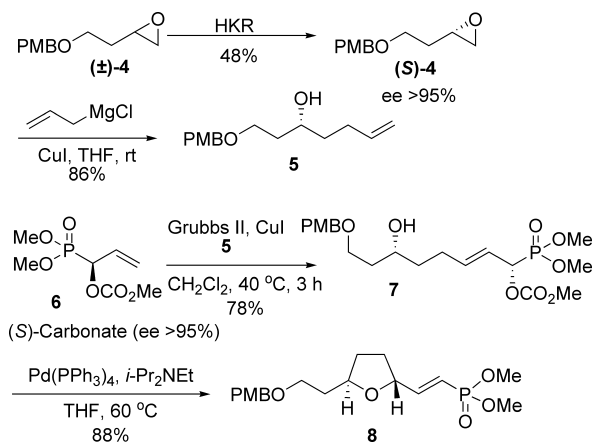


fragment of amphidinolide C (and F).⁴ In this report, we describe the synthesis of the northern C(18)–C(25) fragment and coupling to three side chain aldehydes to form the C(18)–C(34) unit of amphidinolide C, the C(18)–C(29) unit of amphidinolide F, and a synthetic analogue.

The northern C(18)–C(25) fragment contains a 2,5-*trans*-tetrahydrofuran ring. We recently reported a stereospecific approach to cyclic ethers employing cross metathesis of an alkenol and a phosphonoallylic carbonate (derived from acrolein), followed by a Pd(0)-catalyzed cyclization reaction.⁵ The product vinylphosphonates can be oxidized to β -ketophosphonates, which can subsequently undergo Horner–Wadsworth–Emmons (HWE) olefination reactions. This approach appeared ideal for the synthesis of the C(18)–C(34) fragment of amphidinolide C and the C(18)–C(29) fragment of amphidinolide F. In general, it is quite flexible and allows for the synthesis of a variety of side chain analogues for structure–activity relationship studies.

The required alkenol **5** was prepared from PMB-protected 3-buten-1-ol (Scheme 2). Oxidation with mCPBA gave the racemic epoxide ($\pm$)-**4**. The racemic epoxide ($\pm$)-**4** was subjected to hydrolytic kinetic resolution (HKR)⁶ to yield the known (*S*)-epoxide (*S*)-**4**⁷ in >95% enantiomeric excess. Reaction of the (*S*)-epoxide (*S*)-**4** with allylmagnesium chloride and CuI furnished the alkenol **5**.^{7a} The cross

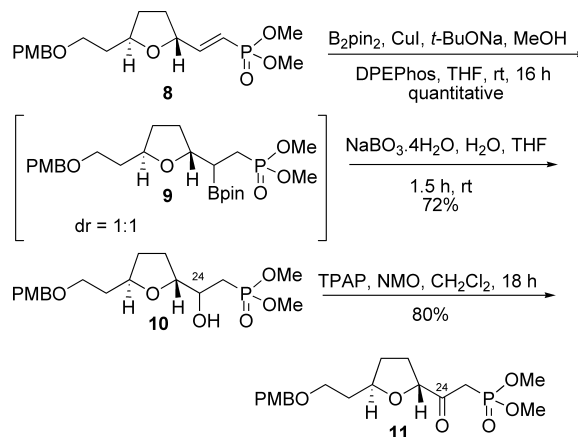
Scheme 2. Synthesis of the 2,5-*trans*-Tetrahydrofuran **8**



metathesis reaction between terminal alkenol **5** and the (*S*)-carbonate **6** (>95% ee) using Grubbs second-generation catalyst and CuI as a cocatalyst proceeded smoothly to give the phosphonoallylic carbonate **7** as the major product in 78% yield⁸ as a $\geq 9:1$ mixture of *E*- and *Z*-isomers, which were inseparable by column chromatography. Palladium(0)-catalyzed cyclization of **7** gave the 2,5-*trans*-tetrahydrofuran-yl-(*E*)-vinylphosphonate **8** in 88% isolated yield together with 5–8% of the undesired *cis* diastereomer.

The next challenge was to convert the vinylphosphonate **8** into β -ketophosphonate **11** (Scheme 3). Initially, Wacker

Scheme 3. Synthesis of the β -Ketophosphonate



oxidation and various modifications were attempted.⁹ Unfortunately, the Wacker oxidation failed to yield the β -ke-

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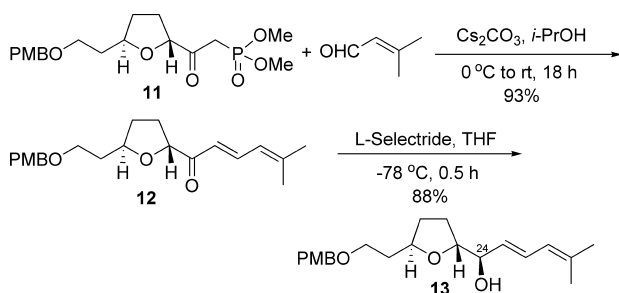
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tophosphonate **11**. However, an alternative protocol employing a hydroboration–oxidation sequence was successful. Hydroboration¹⁰ of the vinylphosphonate **8** using bis(pinacolato)diboron (B₂pin₂), copper(I) iodide, and bis(2-diphenylphosphinophenyl)ether (DPEPhos) as a ligand furnished the desired β -borylated product **9** in quantitative yield as a 1:1 mixture of diastereomers. The formation of a 1:1 diastereomeric mixture was not a problem because of eventual conversion to a ketone. The reproducibility of this reaction proved to be highly dependent on the purity of the reagents.¹¹ Furthermore, the β -borylated product was found to be unstable and underwent β -elimination on standing and on exposure to silica gel. Similar eliminations of alkyl boronates have been observed by others.¹² Consequently, the crude β -borylated product was subjected to sodium perborate (NaBO₃) oxidation without purification to obtain the β -hydroxyphosphonate **10** in 72% over 2 steps. Oxidation of the alcohol was achieved using catalytic tetrapropylammonium perruthenate (TPAP) and NMO to give the β -ketophosphonate **11** in 80% yield and completing the synthesis of the northern C(18)–(25) fragment.

Synthesis of the β -ketophosphonate (northern fragment) **11** sets the stage for Horner–Wadsworth–Emmons (HWE) condensation reaction with a series of aldehydes. The HWE reaction proved more troublesome than originally anticipated. A number of bases and solvents [Ba(OH)₂ in H₂O and THF;¹³ NaH in THF; NaHMDS in THF; *t*-BuOK and 18-crown-6 in THF; LiCl and DBU in CH₂Cl₂,¹⁴ etc.) were screened for the reaction of β -ketophosphonate **11** with 3-methyl-crotonaldehyde (Scheme 4). To our dismay, they

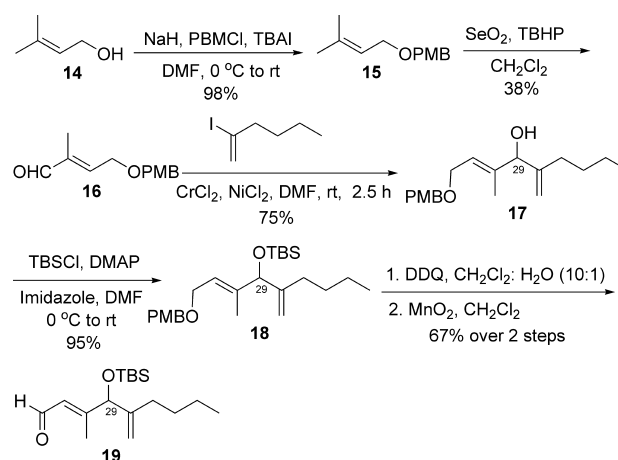
Scheme 4. Synthesis of the C(18)–C(29) Fragment of Amphidinolide F



all failed to yield the desired product. Eventually, optimized reaction conditions using anhydrous K₂CO₃ and 18-crown-6 in toluene¹⁵ gave the desired dienone **12** in an unsatisfactory

38% yield. In an effort to increase the yield, other Group I carbonates and solvents were screened. Finally, a reaction using anhydrous Cs₂CO₃ in dry isopropanol (*i*-PrOH) gave dienone **12** in 93% yield (Scheme 4).¹⁶ Interestingly, reactions using Cs₂CO₃ in CH₃CN or CH₂Cl₂ were unsuccessful. A Felkin–Anh controlled reduction of the dienone **12** at the C(24) position using *L*-selectride¹⁷ yielded the alcohol **13** as a single diastereomer, concluding the synthesis of the C(18)–C(29) unit of amphidinolide F. Other reducing agents, such as NaBH₄, resulted in diastereoisomeric mixtures.

Scheme 5. Synthesis of the Side Chain Aldehyde of Amphidinolide C



Synthesis of the side chain aldehyde **19** (Scheme 5) of amphidinolide C commenced with the PMB protection and subsequent SeO₂ oxidation of the commercially available prenol, **14**, to give the aldehyde **16** in moderate yield. Allylic oxidations with SeO₂ are often low yielding,¹⁸ and in this case, 20–30% of the *Z*-isomer was also formed. A subsequent classic Nozaki–Hiyama–Kishi (NHK) coupling reaction with the aldehyde **16** and 2-iodohexene furnished the alkenol **17** in 75% yield. Further orchestration of the alkenol **17** by *tert*-butylmethylsilyl ether (TBS) protection, oxidative cleavage of the PMB ether, and an allylic oxidation with MnO₂ gave the aldehyde **19**. It should be noted that compound **19** is racemic and will eventually yield C(29) epimers of amphidinolide C. Although not important in this demonstration of the application of the HWE reaction to the synthesis of amphidinolide C and analogues, it should be

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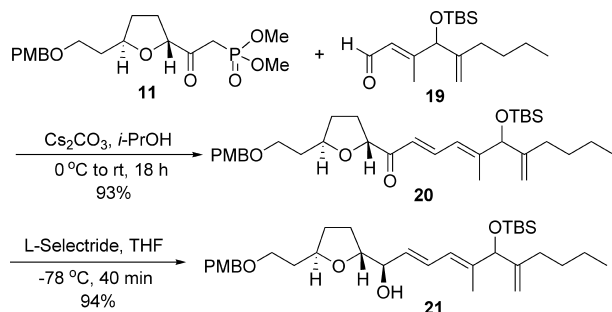
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possible to address the stereochemistry at C(29) using an asymmetric NHK reaction.¹⁹

Again, reaction of the phosphonate **11** with aldehyde **19** using Cs₂CO₃ in *i*-PrOH yielded the dienone **20** in an excellent 93% yield (Scheme 6). Similarly, reduction of the

Scheme 6. Synthesis of the C(18)–C(34) Fragment of Amphidinolide C

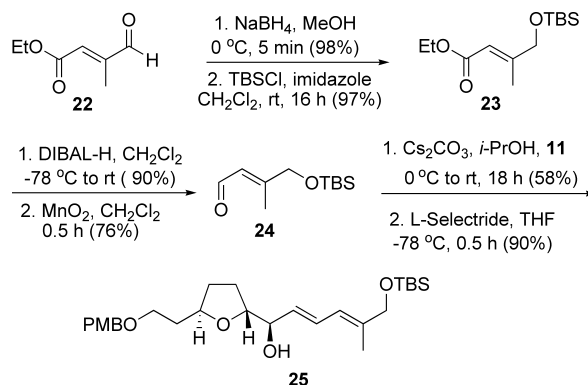


dienone with L-selectride delivered alcohol **21** with the desired stereochemistry as the major diastereomer in 94% yield, completing the synthesis of the C(18)–C(34) fragment of amphidinolide C.

The significant difference in cytotoxicities (approximately 1000-fold) between amphidinolide C and F led us to apply the HWE approach to a synthetic analogue. The preparation of aldehyde **24** proceeded in four straightforward steps from the commercially available oxocrotonate derivative **22** (Scheme 7). The aldehyde **22** was reduced to an alcohol which was protected as a TBS ether **23**. The ester was reduced to an alcohol, which was reoxidized to give aldehyde **24**. HWE olefination reaction of β -ketophosphonate **11** with aldehyde **24** and subsequent reduction by L-selectride furnished the synthetic analogue **25** as the major diastereomer.

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Scheme 7. Synthesis of a Synthetic Analogue



In summary, we have accomplished the synthesis of the C(18)–C(25) northern fragment **11** of amphidinolides C and F via a cross metathesis, Pd(0)-catalyzed cyclization, and hydroboration–oxidation sequence. The northern fragment **11** was coupled to three aldehydes using a HWE olefination reaction to form, after stereoselective reduction, the C(18)–C(29) unit of amphidinolide F **13**, the C(18)–C(34) unit of amphidinolide C **21**, and the synthetic analogue **25**.

Acknowledgment. This work was supported by grant number R01-GM076192 from the National Institute of General Medical studies. We thank Prof. R. K. Winter and Mr. Joe Kramer of the Department of Chemistry and Biochemistry, University of Missouri–St. Louis, for mass spectra and Ms. Hillary Goode and Mr. Donnie Smith of the Department of Chemistry and Biochemistry, University of Missouri–St. Louis, for some preliminary experiments.

Supporting Information Available: Detailed 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>.

OL102345V