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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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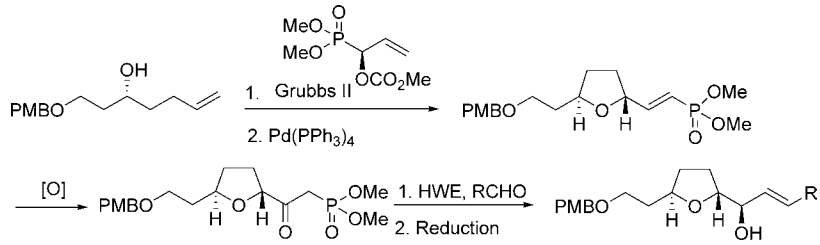
ABSTRACT



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 tetrahydrofuranyl-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 (IC_{50} 0.0058 μg/mL) and human epidermoid carcinoma KB (IC_{50} 0.0046 μg/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)

(1) (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753. (b) Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 9109. (c) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep* **2004**, *21*, 77.

(2) (a) Kobayashi, J.; Ishibashi, M.; Walchi, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490. (b) Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363.

(3) (a) Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4343. (b) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865. (c) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613. (d) Armstrong, A.; Pyrkotis, C. *Tetrahedron Lett.* **2009**, *50*, 3325. (e) Mohapatra, D. K.; Dasari, P. K.; Rahaman, H.; Pal, R. *Tetrahedron Lett.* **2009**, *50*, 6276. (f) Mohapatra, D. K.; Rahaman, H.; Chorghade, M. S.; Gurjar, M. K. *Synlett* **2007**, *4*, 567. (g) Mahapatra, S.; Carter, R. G. *Org. Biomol. Chem.* **2009**, *7*, 4582.

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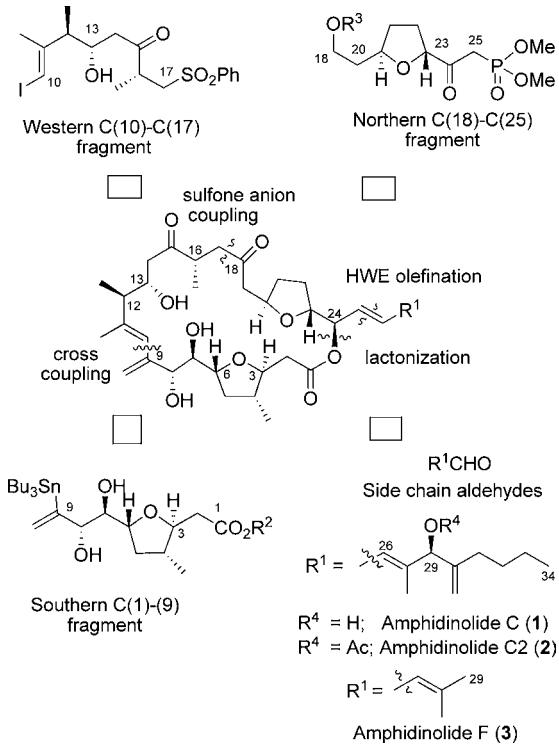
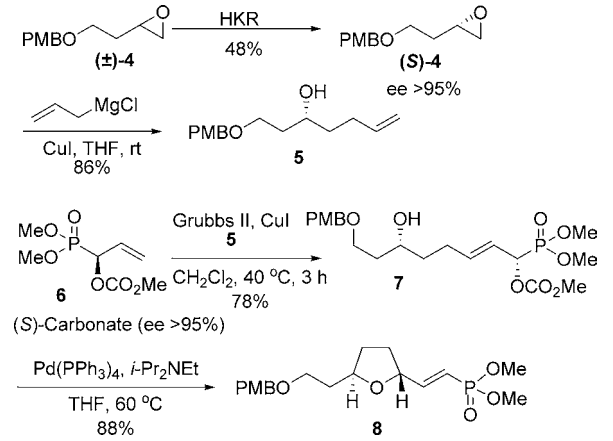
Scheme 1. Retrosynthetic Analysis of Amphidinolide C



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



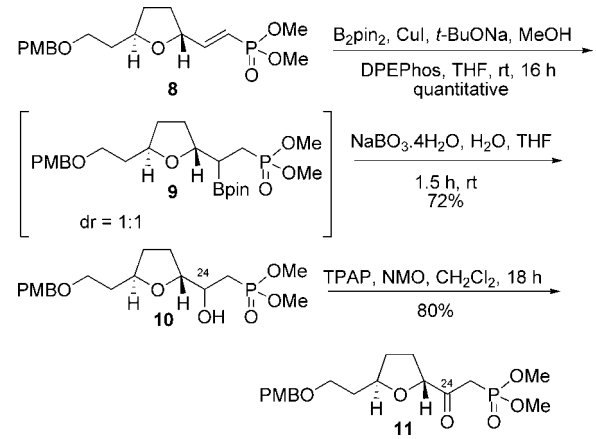
fragment of amphidninolide C (and F).[4] In this report, we describe the synthesis of the northern C(18)−C(25) fragment and coupling to three side chain aldehydes to form the C(18)−C(34) unit of amphidinolide C, the C(18)−C(29) unit of amphidinolide F, and a synthetic analogue.

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 (±)-**4**. The racemic expoxide (±)-**4** was subjected to hydrolytic kinectic 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 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% yield[8] as a ≥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*-tetrahydrofuranyl-(*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-

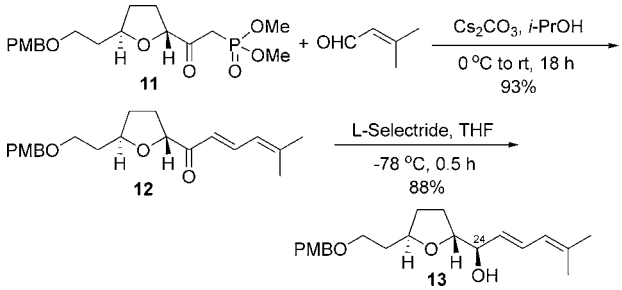
(4) Paudyal, M. P.; Rath, N.P.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 2954.
(5) He, A.; Sutivisedsak, N.; Spilling, C. D. *Org. Lett.* **2009**, *11*, 3124.
(6) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *227*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

(7) The specific rotation value, $[\alpha]_D$, obtained for the nonracemic epoxide **(*S*)-4** contradicted the reported value by Marshall and co-workers but matched that reported by Ley and co-workers (see Supporting Information). (a) Marshall, J. A.; Sabatini, J. *Org. Lett.* **2005**, *7*, 5331. (b) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819.
(8) (a) He, A.; Yan, B.; Thanavaro, A.; Spilling, C. D. *J. Org. Chem.* **2004**, *69*, 8643. (b) Rivard, M.; Blechert, S. *Eur. J. Org. Chem.* **2003**, 2225.

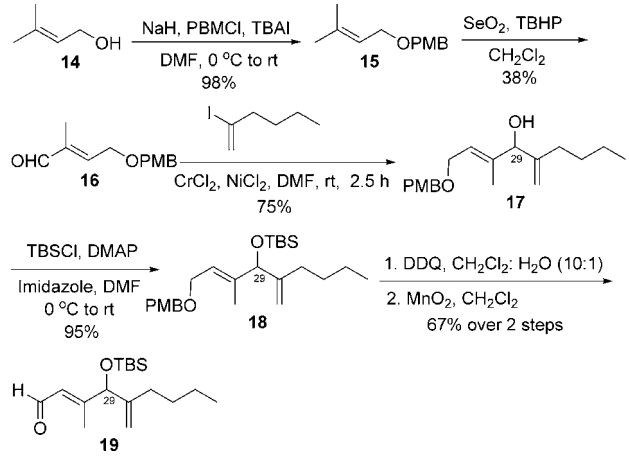
tophosphonate **11**. However, an alternative protocol employing a hydroboration−oxidation sequence was successful. Hydroboration[10] of the vinylphosphonate **8** using bis(pinacolato)diboron (B_2pin_2), copper(I) iodide, and bis(2-diphenylphosphinophenyl)ether (DPEPhos) as a ligand furnished the desired 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 ($NaBO_3$) 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 H_2O and THF;[13] NaH in THF; NaHMDS in THF; *t*-BuOK and 18-crown-6 in THF; LiCl and DBU in CH_2Cl_2,[14] etc.) were screened for the reaction of β-ketophosphonate **11** with 3-methyl-crotonaldehyde (Scheme 4). To our dismay, they all failed to yield the desired product. Eventually, optimized reaction conditions using anhydrous K_2CO_3 and 18-crown-6 in toluene[15] 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 Cs_2CO_3 in dry isopropanol (*i*-PrOH) gave dienone **12** in 93% yield (Scheme 4).[16] Interestingly, reactions using Cs_2CO_3 in CH_3CN or CH_2Cl_2 were unsuccesful. A Felkin−Anh controlled reduction of the dienone **12** at the C(24) position using L-selectride[17] 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 $NaBH_4$, resulted in diastereoisomeric mixtures.

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



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 SeO_2 oxidation of the commercially available prenol, **14**, to give the aldehyde **16** in moderate yield. Allylic oxidations with SeO_2 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 MnO_2 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

(9) (a) Yan, B.; Spilling, C. D. *J. Org. Chem.* **2008**, *73*, 5385. (b) Poss, A. J.; Smyth, M. S. *Synth. Commun.* **1987**, *17*, 1735. (c) Stutz, G.; Pondaven-Raphalen, A. *J. Chem. Res. Synop.* **1980**, 175. (d) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796.

(10) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.

(11) Bis(pinacolato)diboron proved to be the most unstable reagent. It was stored in a glovebox and used up within 6 months.

(12) Maurer, K. W.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 3106.

(13) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

(14) Blenchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(15) Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2346.

(16) Uenishi, J.; Iwamoto, T.; Tanaka, J. *Org. Lett.* **2009**, *11*, 3262.

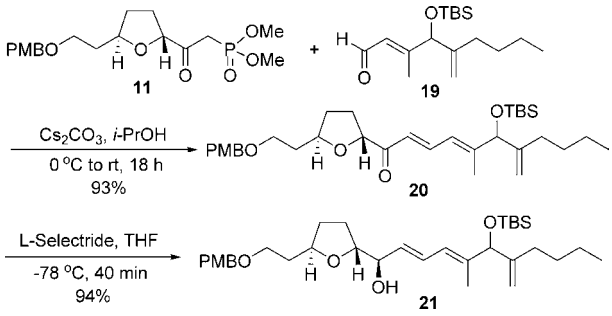
(17) (a) Mohapatra, D. K.; Nayak, S.; Mohapatra, S.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2007**, *48*, 5197. (b) Nicolaou, K. C.; Brenzovich, W. E.; Bulger, P. G.; Francis, T. M. *Org. Biomol. Chem.* **2006**, *4*, 2119.

(18) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Schomaker, J. M.; Geiser, A. R.; Huang, R.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 3794. (c) Maalouf, M. A.; Wiemer, A. J.; Kuder, C. H.; Hohl, R. J.; Weimer, D. *Bioorg. Med. Chem.* **2007**, *17*, 1959.

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

Again, reaction of the phosphonate **11** with aldehyde **19** using Cs_2CO_3 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

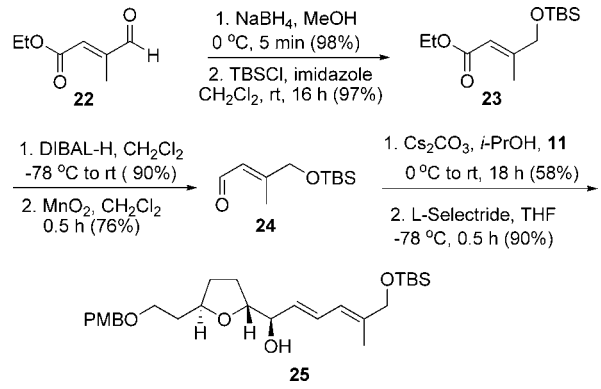


dienone with L-selectride delivered alcohol **21** with the desired stereochemistry as the major diastereomer in 94% yield, completing the synthesis of the C(18)−C(34) fragment of amphidinolide C.

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.

(19) (a) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387. (b) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421. (c) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031. (d) Choi, H.-W.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435.

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**.

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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.

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