Synthetic Studies on Amphidinolide F: Exploration of Macrocycle Construction by Intramolecular Stille Coupling
Ludovic Decultot and J. Stephen Clark*

ABSTRACT: Exploration of an ambitious new strategy for the total synthesis of the cytotoxic marine natural product amphidinolide F is described, which features fabrication of the core structure from four readily accessible fragments and macrocycle construction through C9−C10 bond formation by intramolecular Stille coupling between an alkenyl iodide and alkenyl stannane. Efficient stereoselective synthesis of each of the four building-blocks and subsequent coupling of them to produce the requisite cyclization precursor has been accomplished, but suitable conditions for high-yielding palladium-mediated closure of the macrocycle to produce the fully protected amphidinolide F ring system have yet to be identified.

Amphidinolide F is a structurally complex cytotoxic marine natural product produced by a dinoflagellate of the genus Amphidinium (Figure 1). The isolation of amphidinolide F from cultures of the dinoflagellate and its subsequent characterization were reported by the group of Kobayashi in 1991.1 The complete structure of amphidinolide F and both the relative and absolute configurations of the 11 stereogenic centers embedded in it were assigned by comparison of NMR data with those of key subunits prepared by de novo synthesis.2,3

Amphidinolide F and related amphidinolides are alluring synthetic targets because of their structural complexity and reported biological activities. Myriad synthetic strategies for the stereoselective construction of key fragments of amphidinolide F have been explored in recent years, and many of them are also directly applicable to the synthesis of members of the amphidinolide C series because of the structural similarity of the compounds.4−14 This work has resulted in the total syntheses of amphidinolide F by the groups of Fürstner,15 Carter,16 and Ferrie.17 syntheses of amphidinolides C and C2 have also been completed by these research groups.

We have already reported the synthesis of the C1−C17 and the C18−C29/C18−C34 fragments of amphidinolides F, C, C2, and C3.18 More recently, we have constructed the entire C1−C29 framework of amphidinolide F by a convergent route in which fragments corresponding to C1−C9, C10−C17, and C18−C29 were coupled.19 Although the latter approach delivered the required linear C1−C29 precursor required for formation of the lactone by direct cyclization, problems were encountered when the C1−C17 segment was coupled to the

Received: September 8, 2022
Published: October 12, 2022
C18−C29 fragment at a late stage in the synthesis, and so the alternative synthetic strategy described herein was explored.

The new strategy evolved from a retrosynthetic analysis of amphidinolide F in which the core structure is disconnected to produce four fragments (i−iv) of variable size and complexity (Figure 1). The two most complex fragments (i and iv) each contain a single tetrahydropyran and are similar in structure to intermediates used in our recently published study. The C19−C29 fragment, which corresponds to fragment iv in the retrosynthetic analysis, was prepared as shown in Scheme 1.

Scheme 1. Preparation of the C19−C29 Fragment

The route commenced with the known 2,5-disubstituted tetrahydrofuran 1, which was prepared directly from an open chain γ-hydroxyalkene by use of a modified version of Mukaiyama’s cobalt-catalyzed oxidative cyclization reaction, in the manner described by Pagenkopf and co-workers.20,21 The alcohol 1 was subjected to oxidation, and the resulting aldehyde was reacted with a Grignard reagent generated from trimethylsilylacetylene. Removal of the trimethylsilyl group followed by quenching with iodine according to Negishi’s protocol,22 as performed by Maier and co-workers on an analogous alkyne.23 Subsequent nucleophilic displacement with lithiated 1,3-dithiane afforded the C14−C18 fragment 9 suitable for attachment to the C19−C29 fragment.

Synthesis of the C14−C18 fragment that corresponds to fragment iii in the retrosynthetic analysis (Figure 1) commenced with the known β-hydroxy ester 7, which was prepared by Fráter−Seebach alkylation of commercially available methyl (R)-3-hydroxybutyrate (Scheme 2).24 The hydroxyl group of the β-hydroxy ester 7 was first protected as the 1-ethoxymethyl ether and the ester group was reduced with lithium aluminum hydride to provide the primary alcohol 8. The alcohol was converted into the corresponding iodide, and subsequent nucleophilic displacement with lithiated 1,3-dithiane afforded the C14−C18 fragment 9 suitable for attachment to the C19−C29 fragment.

The starting compound for synthesis of the C10−C13 fragment was the known alkyne 10, which was prepared from commercially available methyl (S)-3-hydroxy-2-methyl-butyrate by a five-step sequence, analogous to that described by Lee and co-workers (Scheme 3).26 The alkyne 10 was converted into the alkenyl iodide 11 by zirconium-mediated carboalumination followed by quenching with iodine according to Negishi’s protocol,27 as performed by Maier and co-workers on an analogous alkyne.28 Subsequent cleavage of the silyl ether delivered the alcohol 12. Treatment with Dess–Martin periodinane produced the aldehyde 13, which corresponds to fragment ii in the retrosynthetic analysis (Figure 1).

Scheme 2. Preparation of the C14−C18 Fragment

The final fragment—C1−C9—required for the synthesis was obtained by functionalization of the ester 14, a compound we had used in our previously published work on the synthesis of amphidinolide F (Scheme 4).29 Thus, reductive cleavage of the pivaloyl group from the ester 14 afforded the alcohol 15. Dess–Martin oxidation of the alcohol 15 to give the aldehyde 16 and subsequent Pinnick oxidation delivered the carboxylic acid 17 (fragment i in Figure 1).25,26

Completion of the syntheses of the C1−C9, C10−C13, C14−C18, and C19−C29 fragments allowed construction of the complete framework of amphidinolide F to be explored. Coupling commenced with attachment of the C14−C18 fragment to the C19−C29 fragment (Scheme 5). The alcohol 6 was first converted into the corresponding iodide by treatment with iodine and triphenylphosphine. Subsequent
Fragment coupling was accomplished by nucleophilic attack of the iodide with the anion generated by deprotonation of the dithiane 9 with tert-butyllithium. Removal of the ethoxyethyl protecting group from the coupled product 18 under acidic conditions delivered the alcohol 19 in 44% yield over three steps. Parikh–Doering oxidation of the alcohol produced the ketone 20 and subsequent removal of the TBS protecting group revealed the alcohol 21, which was immediately reprotected as the more labile triethylsilyl (TES) ether to give the ketone 22.

Ketone 22 corresponds to the C14–C29 segment of the natural product and possesses the requisite functionality for attachment of the C10–C13 fragment by an aldol condensation reaction (Scheme 6). Generation of a boron enolate by treatment of the methyl ketone 22 with dicyclohexylboron chloride and triethylamine followed by addition of the aldehyde 13 at −78 °C afforded the diastereomeric alcohols 23a and 23b (2.2:1). The configuration at the newly created hydroxyl-bearing stereogenic center was made by conversion of the alcohol 23a into diastereomeric Mosher esters and subsequent 1H NMR analysis according to the protocol of Hoye and co-workers (see the Supporting Information). Chromatographic separation of the alcohols was challenging, but samples of each diastereomer were isolated and then protected as TBS ethers to give the ketones 24a and 24b.

Construction of the C10–C29 segment meant that coupling to the C1–C9 fragment to produce the entire C1–C29 framework of amphidinolide F could be explored. The first approach that was investigated involved direct intermolecular Stille coupling of the vinylic stannanes 15 and 17, corresponding to the C1–C9 fragment, to the C10–C29 iodide 24b (Scheme 7). In recent studies performed by us, Stille coupling had been used to attach the vinylic stannane 14 (Scheme 4) to a truncated C10–C17 fragment. This reaction had proceeded in high yield, and so the proposed coupling reaction was not expected to be problematic. However, when the reagents and conditions used previously were employed perform Stille coupling between the alkenyl iodide 24b and either vinylic stannane 15 or 17, neither of the expected coupled products 25 or 26 was obtained. The failure of the coupling reaction was both unexpected given that Ferrié and co-workers were able to couple the vinylic stannane 17 to a very closely related analogue of the C10–C29 segment 24b under similar reaction conditions during their recent synthesis of amphidinolide F. Alternative Stille reaction conditions are clearly required to accommodate the bulky alkenyl iodide 24b and/or the acidic coupling partners 15 and 17.

The failure of the direct intermolecular Stille coupling reaction to deliver either of the expected coupled products (25 or 26) corresponding to the C1–C29 framework of amphidinolide F meant that a new endgame strategy was required. The decision was made to investigate an alternative route in which the reactions used to assemble the complete carbon framework and construct the macrocycle were

---

Scheme 4. Functionalization of the C1–C9 Fragment

Scheme 5. Fragment Coupling to Produce the C14–C29 Segment

Scheme 6. Construction of the C10–C29 Segment

Scheme 7. Attempted Intermolecular Stille Coupling of the C1–C9 Fragment to the C10–C29 Segment

Stille coupling had been used to attach the vinylic stannane 14 (Scheme 4) to a truncated C10–C17 fragment. This reaction had proceeded in high yield, and so the proposed coupling reaction was not expected to be problematic. However, when the reagents and conditions used previously were employed perform Stille coupling between the alkenyl iodide 24b and either vinylic stannane 15 or 17, neither of the expected coupled products 25 or 26 was obtained. The failure of the coupling reaction was both unexpected given that Ferrié and co-workers were able to couple the vinylic stannane 17 to a very closely related analogue of the C10–C29 segment 24b under similar reaction conditions during their recent synthesis of amphidinolide F. Alternative Stille reaction conditions are clearly required to accommodate the bulky alkenyl iodide 24b and/or the acidic coupling partners 15 and 17.

The failure of the direct intermolecular Stille coupling reaction to deliver either of the expected coupled products (25 or 26) corresponding to the C1–C29 framework of amphidinolide F meant that a new endgame strategy was required. The decision was made to investigate an alternative route in which the reactions used to assemble the complete carbon framework and construct the macrocycle were
reordered. We opted for an approach in which an ambitious intramolecular Stille coupling reaction would be employed to accomplish simultaneous formation of the complete carbon framework and the macro lactone in a single operation (Scheme 8). To investigate this approach, the C18 carbonyl group and the C24 hydroxyl group in the C10−C29 segment 24a (Scheme 6) were unmasked by hydrolysis of the dithiane group under standard conditions with concomitant cleavage of the TES ether. The resulting alcohol 27 was then subjected to esterification with the carboxylic acid 17 under standard Yamaguchi conditions to produce the ester 28 in good yield. Intramolecular Stille coupling to produce the macrolactone 29 was then explored. Global deprotection of the lactone 29 would deliver 13-epi-amphidinolide F, and it was anticipated that the diastereomeric compound 24b would be subjected to a parallel sequence of reactions to give amphidinolide F. Attempted intramolecular Stille coupling reaction of the ester 28 to give the lactone 29 produced a complex mixture of products, and so we attempted to isolate 13-epi-amphidinolide F by immediate deprotection of the crude material. However, the required product was not isolated after complete silyl ether cleavage to reveal the free hydroxyl groups at C7, C8, and C13.

In summary, an innovative new strategy for the total synthesis of the amphidinolide F has been investigated in which macrocycle formation was to be accomplished by an intramolecular Stille coupling reaction. Fragments that correspond to C1−C9, C10−C13, C14−C18, and C19−C29 units were prepared from readily available starting materials in an efficient and stereoselective manner, and then coupled to provide the substrate required for the proposed macrocyclization reaction. A limited number of reaction conditions have been explored for the intramolecular Stille coupling reaction to give fully protected amphidinolide F. However, further studies are required to identify the appropriate palladium catalyst and reaction conditions necessary to effect high-yielding macrocyclization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03045.

Experimental procedures for preparation of all new compounds along with characterization data and copies of 1H and 13C NMR spectra (DOCX)

AUTHOR INFORMATION

Corresponding Author

J. Stephen Clark – School of Chemistry, University of Glasgow, Glasgow G12 8QQ, U.K.; orcid.org/0000-0003-3935-0377; Email: stephen.clark@glasgow.ac.uk

Author

Ludovic Decultot – School of Chemistry, University of Glasgow, Glasgow G12 8QQ, U.K.; Present Address: Syros Pharmaceuticals, 35 CambridgePark Drive, Fourth Floor, Cambridge, Massachusetts 02140, United States; orcid.org/0000-0002-2607-2016

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c03045

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Dr. Ian Sword for generously providing full financial support to L.D. during his Ph.D. studies.

REFERENCES

(1) Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. Amphidinolide F, A New Cytotoxic Macrolide from the Marine Dinoflagellate Amphidinium sp. J. Antibiot. 1991, 44, 1259−1261.

(2) (a) Kobayashi, J.; Ishibashi, M.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. Amphidinolide C: The First 25-Membered Macro cyclic Lactone with Potent Antineoplastic Activity from the Cultured Dinoflagellate Amphidinium sp. J. Am. Chem. Soc. 1988, 110, 490−494. (b) Kubota, T.; Tsuda, M.; Kobayashi, J. Absolute Stereochemistry of Amphidinolide C. Org. Lett. 2001, 3, 1363−1366.

(3) Kubota, T.; Tsuda, M.; Kobayashi, J. Absolute Stereochemistry of Amphidinolide C: Synthesis of C-1−C-10 and C-17−C-29 Segments. Tetrahedron 2003, 59, 1613−1625.

(4) (a) Shotwell, J. B.; Roush, W. R. Synthesis of the C11−C29 Fragment of Amphidinolide F. Org. Lett. 2004, 6, 3865−3868. (b) Bates, R. H.; Shotwell, J. B.; Roush, W. R. Stereoselective Syntheses of the C(1)(1)−C(9)(1) Fragment of Amphidinolide C. Org. Lett. 2008, 10, 4343−4346.

(5) (a) Mohapatra, D. K.; Rahaman, H.; Chorghade, M. S.; Gurjar, M. K. Synthesis of the C19−C34 Segment of Amphidinolide C. Synlett 2007, 4, 567−570. (b) Mohapatra, D. K.; Dasari, P.; Rahaman, H.; Pal, R. Stereoselective Synthesis of the Densely Functionalized C1−C9 Fragment of Amphidinolides C and F. Tetrahedron Lett. 2009, 50, 6276−6279.

(6) Armstrong, A.; Pyrktosis, C. Synthetic Studies on Amphidinolides C and F: Synthesis of the C18−C29 Segment of Amphidinolide F. Tetrahedron Lett. 2009, 50, 3325−3328.

(7) Mahapatra, S.; Carter, R. G. Efficient Synthesis of the C-17−C-29 Subunit of Amphidinolides C and F. Org. Biomol. Chem. 2009, 7, 4582−4585.

(8) (a) Paudyal, M. P.; Rath, N. P.; Spilling, C. D. A Formal Synthesis of the C1−C9 Fragment of Amphidinolide C Employing

![Scheme 8. Attempted Simultaneous Construction of the C1−C29 Framework and the Macrolactone](image-url)
the Tamara Reaction. *Org. Lett.* **2010**, *12*, 2954−2957. (b) Roy, S.; Spilling, C. D. Synthesis of the C(18)−C(34) Fragment of Amphidinolide C and the C(18)−C(29) Fragment of Amphidinolide F. *Org. Lett.* **2010**, *12*, 5326−5329.

(9) Ferrié, L.; Figadère, B. Efficient Synthesis of the C(1)−C(9) Fragment of Amphidinolides C, C2, and F. *Org. Lett.* **2010**, *12*, 4976−4979.

(10) (a) Morra, N. A.; Pagenkopf, B. L. Gram Scale Synthesis of the C(34) Fragment of Amphidinolide C. *Org. Lett.* **2011**, *13*, 572−575. (b) Pagenkopf, B. L.; Morra, N. A. Synthesis of the C(1)−C(9) Fragment of Amphidinolide C. *Tetrahedron* **2013**, *69*, 8632−8644.

(11) (a) Wu, D.; Forsyth, C. J. Synthesis of the C1−C14 and C15−C25 Fragments of Amphidinolide C. *Org. Lett.* **2013**, *15*, 1178−1181. (b) Akwaboah, D. C.; Wu, D.; Forsyth, C. J. Stereoselective Synthesis of the C1−C9 and C11−C25 Fragments of Amphidinolides C, C2, C3, and F. *Org. Lett.* **2017**, *19*, 1180−1183.

(12) Su, Y.-X.; Dai, W.-M. Synthesis of the C18−C26 Tetrahydrofuran-Containing Fragment of Amphidinolide C Congeners via Tandem Asymmetric Dihydroxylation and S2O2 Cyclization. *Tetrahedron* **2018**, *74*, 1546−1554.

(13) Namirembe, S.; Yan, L.; Morken, J. P. Studies toward the Synthesis of Amphidinolide C1: Stereoselective Construction of the C(1)−C(15) Segment. *Org. Lett.* **2020**, *22*, 9174−9177.

(14) Williams, D. R.; De, R.; Fultz, M. W.; Fischer, D. A.; Morales-Ramos, A.; Rodriguez-Reyes, D. Studies of the Enantiocontrolled Synthesis of the C(10)−C(25) Subunit of Amphidinolide C. *Org. Lett.* **2020**, *22*, 4118−4122.

(15) (a) Valot, G.; Regens, C. S.; O’Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. Total Synthesis of Amphidinolide F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9534−9538. (b) Valot, G.; Mailhol, D.; Regens, C. S.; O’Malley, D. P.; Godineau, E.; Takikawa, H.; Philippps, F.; Fürstner, A. Concise Total Syntheses of Amphidinolides C and F. *Chem. Eur. J.* **2015**, *21*, 2398−2408.

(16) (a) Mahapatra, S.; Carter, R. G. Enantioselective Total Synthesis of Amphidinolide F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7948−7951. (b) Mahapatra, S.; Carter, R. G. Exploiting Hidden Symmetry in Natural Products: Total Syntheses of Amphidinolides F and C. *J. Am. Chem. Soc.* **2013**, *135*, 10792−10803.

(17) (a) Ferrié, L.; Fenneteau, J.; Figadère, B. Total Synthesis of the Marine Macroide Amphidinolide F. *Org. Lett.* **2018**, *20*, 3192−3196. (b) Ferrié, L.; Ciss, I.; Fenneteau, J.; Vallortotto, S.; Seck, M.; Figadère, B. Amphidinolides F and C2: An Odyssey in Total Synthesis. *J. Org. Chem.* **2022**, *87*, 1110−1123.

(18) (a) Clark, J. S.; Yang, G.; Osnowski, A. P. Synthesis of the C-1−C17 Fragment of Amphidinolides C, C2, C3, and F. *Org. Lett.* **2013**, *15*, 1460−1463. (b) Clark, J. S.; Yang, G.; Osnowski, A. P. Synthesis of the C18−C34 Fragment of Amphidinolides C, C2, and C3. *Org. Lett.* **2013**, *15*, 1464−1467.

(19) Romiti, F.; Decultot, L.; Clark, J. S. Convergent Synthesis of the C1−C29 Framework of Amphidinolide C. *J. Org. Chem.* **2022**, *87*, 8126−8141.

(20) Inoki, S.; Mukaiyama, T. A Convenient Method for the Stereoselective Preparation of trans-2-Hydroxymethyltetrahydrofurans by the Oxidative Cyclization of 5-Hydroxy-1-alkenes with Molecular Oxygen Catalyzed by Cobalt(II) Complex. *Chem. Lett.* **1990**, *19*, 67−70.

(21) Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B. L. Increased Yields and Simplified Purification with a Second-Generation Cobalt Catalyst for the Oxidative Formation of trans-THF Rings. *Org. Lett.* **2009**, *11*, 5614−5617.

(22) Alami, M.; Ferri, F.; Linstrumelle, G. An Efficient Palladium-Catalysed Reaction of Vinyl and Aryl Halides or Triflates with Terminal Alkynes. *Tetrahedron Lett.* **1993**, *34*, 6403−6406.

(23) Marshall, J. A.; Audia, J. E.; Grote, J. Acyclic Stereoregulation in Catalyzed Intramolecular Diels–Alder Cyclizations of 4-Methyl-2,8,10-undecatrienals. *J. Org. Chem.* **1986**, *51*, 1155−1157.

(24) Suzuki, T.; Chida, N. The New and Efficient Synthetic of a Hep-tose Moiety of Spicamycin. *Chem. Lett.* **2003**, *32*, 190−191.

(25) (a) Fräter, G. Über die Stereospezifität der α-Alkylierung von β-Hydroxy-carbonsäureestern. *Helv. Chim. Acta* **1979**, *62*, 2825−2828. (b) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966−3979.

(26) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. Total Synthesis of (−)-Amphidinolide E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019−8021.

(27) Negishi, E.; Van Horn, D. E.; Yoshiida, T. Carbometalation Reaction of Alkynes with Organoalane-Zirconocene Derivatives as a Route to Stereo- and Regiodefined Trisubstituted Alkenes. *J. Am. Chem. Soc.* **1985**, *107*, 6639−6647.

(28) Rink, C.; Navickas, V.; Maier, M. E. An Approach to the Core Structure of Leiodermatolide. *Org. Lett.* **2011**, *13*, 2334−2337.

(29) Høye, T. B.; Jeffrey, C. S.; Shao, F. Mosher Ester Analysis for the Determination of Absolute Configuration of Stereogenic (Chiral) Carbonil Carbons. *Nat. Protoc.* **2007**, *2*, 2451−2458.

(30) (a) Nicolau, K. C.; Chakraborty, T. K.; Piscipio, A. D.; Minowa, N.; Bertinato, P. Total Synthesis of Rapamycin. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420. (b) Brodmann, T.; Janssen, D.; Kalesse, M. Total Synthesis of Chivosazole F. *J. Am. Chem. Soc.* **2010**, *132*, 13610−13611.

(31) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A. Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-Ring Lactonization. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.