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Studies toward the Synthesis of Amphidinolide C1: Stereoselective Construction of the C(1)−C(15) Segment

Sheila Namirembe, Lu Yan, and James P. Morken*

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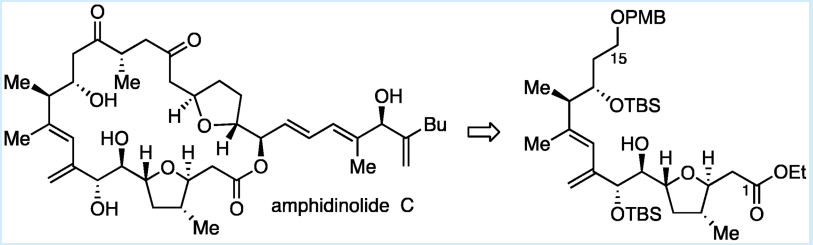

ABSTRACT: An enantioselective synthesis of the C(1)−C(15) segment of the marine natural product amphidinolide C has been accomplished by a route that includes a stereoselective boron−Wittig reaction to furnish a trisubstituted alkenylboronate. In addition, the route employs enantioselective alkene diboration to install the C(6) hydroxyl group which undergoes intramolecular conjugate addition to establish a tetrahydrofuran ring. Lastly, a catalytic Suzuki−Miyaura cross-coupling is accomplished to construct the C(9)−C(10) bond.

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Amphidinolides are a large family of macrolide natural products isolated from dinoflagellates *Amphidinium* sp.[1] As of this writing, more that 40 compounds have been isolated from this organism by the Kobayashi group with amphidinolide C1 (**1**, Figure 1) being a unique structure.[2] As shown in Figure 1, the bioactivity of the C1 macrolactone is very high with an IC_{50} of 8 nM versus L1210 cells. Interestingly, very subtle changes to the C1 structure lead to significant erosion of cytotoxicity: protection of the C(29) hydroxyl group (amphidinolide C2, **2**) or removal of the C(8) hydroxyl (amphidinolide C4, **3**) leads to a 100-fold loss in potency as does alteration of the macrolide side chain (amphidinolide F, **4**).[3] Many other amphidinolides possess nanomolar potency against cancer cell lines, and nearly all of the cytotoxic examples bear alkenyl epoxide functional groups such as that present in amphidinolide H (**5**).[4] Amphidinolide H has been shown to covalently modify actin, an activity that is thought to originate from the electrophilicity of the alkenyl epoxide group.[5] That amphidinolide C1 can retain potency while not enjoying the added binding ability proffered by a highly electrophilic functional group has made this compound a target of interest. Subsequent to Kobayashi's reports on the isolation, structural elucidation[2] and absolute stereochemistry[6] of amphidinolide C1, several groups have worked toward its efficient chemical synthesis. In addition to a number of fragment studies,[7] completed total synthesis have been recorded by teams from the Fürstner[8] and Carter[9] laboratories. In this report, we describe our approach to the C(1)−C(15) segment of amphidinolide C1 via a combination of catalytic synthetic methods.

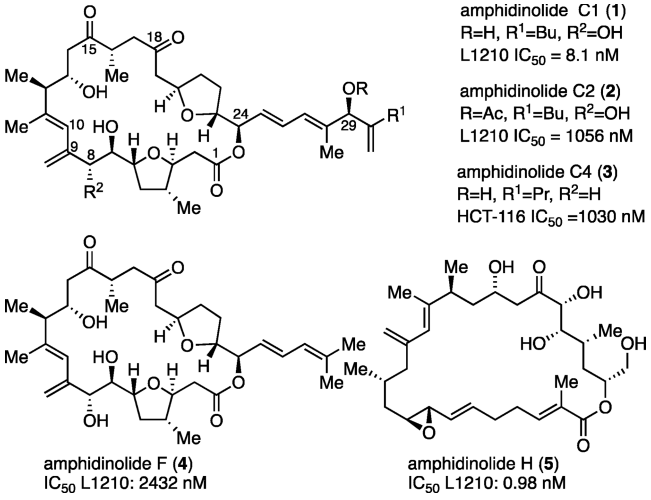

Figure 1. Structure and bioactivity of several members of the amphidinolide family of marine natural products.

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Our interest in amphidinolide C stems from its biological activity and the challenges posed by its efficient and practical synthesis. To address the target, we planned to employ a Yamaguchi esterification[10] to complete the lactone and to join fragments **A** and **B** (Figure 2) by a nitroalkane conjugate

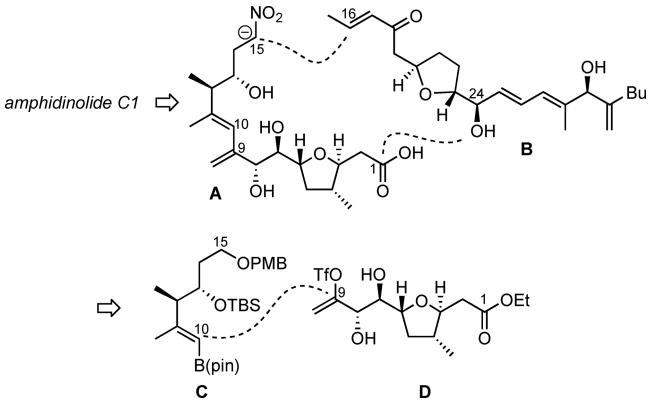


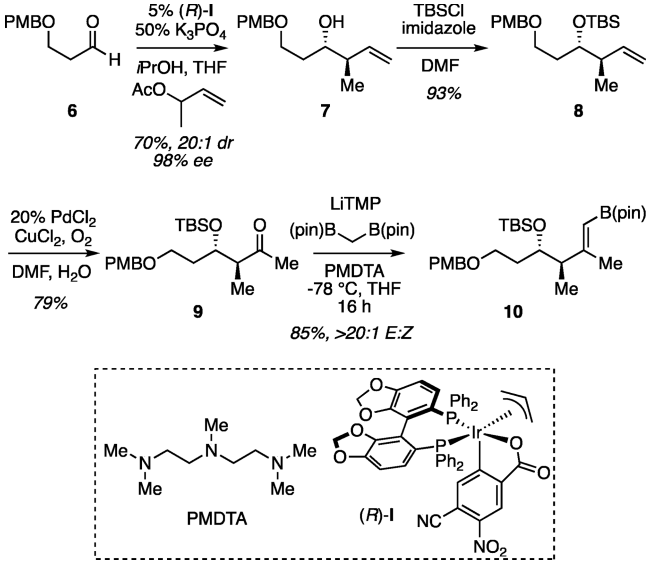
Figure 2. Synthetic approach to the construction of amphidinolide C1 from smaller fragments.

addition[11]/Nef reaction.[12] Fragment **A** represents the C(1) to C(15) segment of amphidinolide C and might be accessible by transition metal-catalyzed cross-coupling of fragments **C** and **D** to connect C(9) with C(10). Of note, a cross-coupling approach was employed by the Fürstner team to connect C(9) and C(10), albeit a Stille reaction was employed whereas we wished to examine the utility of the Suzuki–Miyaura reaction to establish this linkage. Lastly, the synthesis of the individual **C** and **D** fragments, as delineated below, was accomplished using boron-based methodology as described by our laboratories.

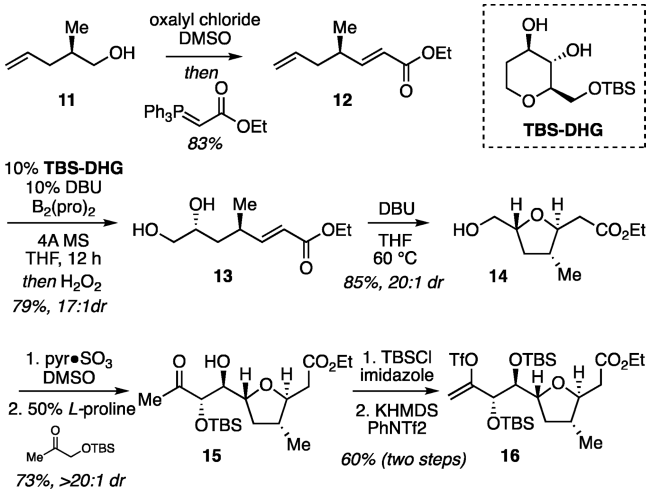
To synthesize fragment **C** in a catalytic enantioselective fashion, we considered the Krische *anti* crotylation[13] as a scalable and reliable method for efficient construction of the two stereogenic centers. Thus, aldehyde **6** was employed as substrate under reducing conditions with 2-propanol as reductant and iridium complex (*R*)-**I** as the catalyst (Scheme 1). This process furnished alcohol **7** in good yield and with excellent stereoselectivity (98% ee). While synthesis of trisubstituted alkenyl boronates such as that which appears in compound **10** can be effected by alkyne carbometalation/borylation,[14] this process employs potently pyrophoric trimethylaluminum as a requisite reagent. As an alternative, we considered the boron–Wittig reaction of ketones that was recently established in our laboratory.[15] Thus, after hydroxyl protection, compound **8** was subjected to Wacker oxidation[16] of the terminal alkene, which delivered ketone **9** in good yield. Using the recently reported modified boron–Wittig reaction,[15] we converted ketone **9** into the desired alkenyl boronic ester **10** in high yield and excellent diastereoselectivity. ^{1}H NMR NOESY analysis was used to establish the *E* configuration of the olefin (see the Supporting Information for details).

To access fragment **D** (compound **16**, Scheme 2), we started with readily accessible known alcohol **11**.[17] Alcohol **11** underwent a Swern oxidation[18] to afford an aldehyde which was directly subjected to stabilized-Wittig olefination[19] to furnish known unsaturated ester **12**.[20] At this juncture, we applied the recently developed carbohydrate and DBU co-catalyzed diboration[21] to terminal alkene **12** which enabled formation of diol **13** in good yield and diasteroselectivity. To

Scheme 1. Synthesis of the C(10)–C(16) (10) Segment of Amphidinolide C1



Scheme 2. Synthetic Approach to the Construction of Amphidinolide C1 from Smaller Fragments



access the *trans* tetrahydrofuran ring, we considered base-promoted cyclization according to a stereoselectivity model proposed by Roush.[7c] After investigating a number of bases and reaction conditions, it was found that reaction in the presence of DBU at 60 °C promoted the intramolecular cyclization of **13** to give *trans*-disubstituted tetrahydrofuran **14** in good yield and diastereoselectivity. Completion of the synthesis of fragment **16** employed Parikh–Doering oxidation[22] to transform alcohol **14** into the derived aldehyde which, given its instability, was immediately subjected to proline-catalyzed aldol reaction with α-siloxyacetone to give **15**. This procedure was employed by Fürstner[8] and, with slight modification was found to be effective for the production of **15**. After silyl protection of **15** the ketone was deprotonated with KHMDS and then treated with Comins' reagent[23] to furnish the alkenyl triflate **16** in moderate yield.

Previous syntheses of amphidinolide C and F have relied on the Stille cross-coupling to construct the diene motif. While this methodology is feasible, it utilizes toxic organotin reagents and might pose a safety concern on large scale. To the best of

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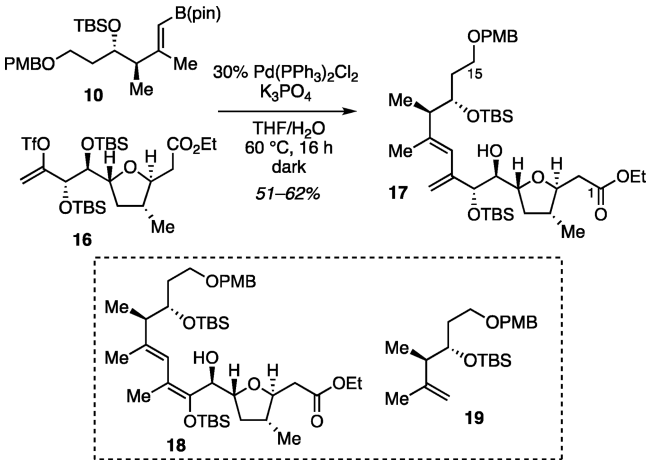
our knowledge, the Suzuki−Miyaura cross-coupling with appropriate alkenyl derivatives has not been employed in the construction of amphidinolide targets. Moreover, through the use of the boron−Wittig reaction, ample material was available to explore this strategy. During these studies, a number of conditions were investigated to execute the Suzuki−Miyaura cross-coupling. During the course of the optimization studies, it was found that the amount of protodeboronation product (**19**, Scheme 3) was affected by the amount of base. In

Scheme 3. Suzuki Coupling Reaction to Assemble the C(1)−C(15) Fragment of Amphidinolide C



addition, the amount of isomerized product **18** was influenced by the nature of the base and light. After optimization, we found that Pd(dppf)Cl_2, K_3PO_4, THF/H_2O, and reaction at 60 °C in the dark provided the desired cross coupling product in 52−61% isolated yield. During the course of the reaction, the silyl ether group at C(7) was cleaved to generate alcohol **17** as the product. This outcome is expected to be inconsequential to the ultimate synthesis strategy.

In conclusion, we have accomplished the synthesis of the C(1)−C(15) segment of amphidinolide C. The key steps included a catalytic and enantioselective *anti* Krische crotylation and a modified boron-Wittig olefination. Also critical were the carbohydrate/DBU co-catalyzed diboration and an organocatalytic *anti* aldol reaction. This report also describes the first time a Suzuki−Miyuara cross-coupling has been demonstrated to assemble two advanced intermediates for the synthesis amphidinolide C. An important aspect of the cross-coupling is that it should be done in the absence of light; otherwise, isomerization of the product diene occurs. Collectively, the knowledge gained from the syntheses described above will assist in completion of amphidinolide C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03134.

Procedures, characterization, spectral and chromatographic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

James P. Morken − *Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States;* orcid.org/0000-0002-9123-9791; Email: morken@bc.edu

Authors

Sheila Namirembe − *Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States*

Lu Yan − *Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03134

Notes

The authors declare no competing financial interest.

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