

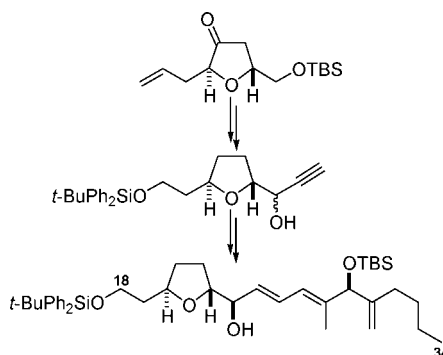
Synthesis of the C-18–C-34 Fragment  
of Amphidinolides C, C2, and C3

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## ABSTRACT



The C-18–C-34 fragment of amphidinolides C, C2, and C3 and the C-18–C-29 fragment of amphidinolide F have been constructed from a *trans*-2,5-disubstituted dihydrofuran. This key intermediate was prepared from a dihydrofuranone formed by diastereoselective rearrangement of a free or metal-bound oxonium ylide generated from a metal carbenoid. The side chains found in amphidinolides C and F were introduced using Sonogashira coupling reactions.

The amphidinolides are macrolide natural products extracted from symbiotic dinoflagellates of the genus *Amphidinium* cultivated from the Okinawan flatworms of the *Amphiscolops* species. Several members of this diverse group of macrolides exhibit potent cytotoxicity and possess other biological activities, but in most cases the substantial quantities of material required in order to fully establish their therapeutic potential are not available.<sup>1</sup> Amphidinolide C<sup>2</sup> (1) and the closely related congeners amphidinolides C2<sup>3</sup> (2), C3<sup>4</sup> (3), and F<sup>5</sup> (4) are particularly

attractive targets for total synthesis because of their powerful *in vitro* activities and the synthetic challenges that their complex molecular architectures present (Figure 1). Several groups have reported syntheses of fragments of these natural products,<sup>2b–d,6</sup> but only very recently has a total synthesis of one member of the family, amphidinolide F (4), been published.<sup>7</sup>

Amphidinolide C was isolated by Kobayashi et al. in 1988 and was found to possess cytotoxic activity against both murine lymphoma and epidermoid carcinoma KB cell lines.<sup>2</sup> Subsequently, the absolute and relative configurations of this and the other natural products in the series were established and their bioactivities were determined,

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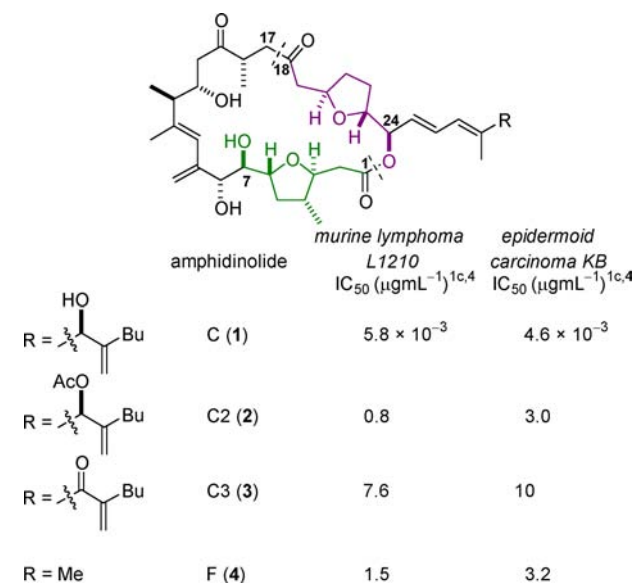
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providing insights into the structure–activity relationships (SARs) within this unique set of compounds.



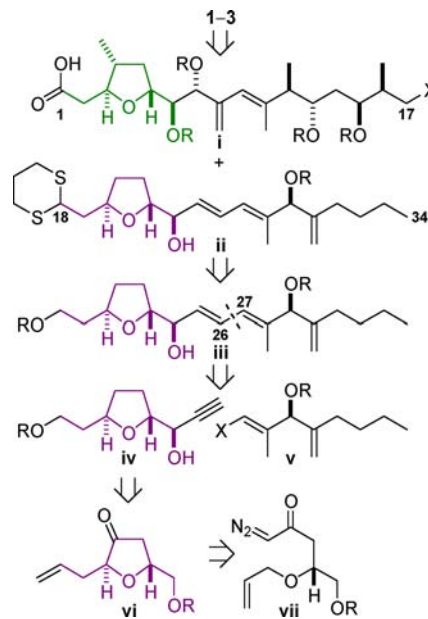
**Figure 1.** Amphidinolides C, C2, C3, and F.

The 25-membered macrolactone core of amphidinolide C contains two 2,5-*trans* substituted tetrahydrofurans embedded in its structure and an unsaturated side chain (C-25 to C-34). The significant differences in biological activity between amphidinolides C, C2, and F result from structural variations in the side-chain region of these compounds.<sup>1</sup> The C-29 hydroxyl group confers potent bioactivity on amphidinolide C, and the absence of this substituent or removal of its H-bond donor capacity by acetylation results in a 1000-fold reduction in activity (Figure 1). This observation regarding the SAR encouraged us to adopt a modular synthetic approach in which the side chain of amphidinolide C and analogues would be constructed using Pd-catalyzed coupling reactions.

The retrosynthetic analysis of amphidinolide C is shown in Scheme 1. Initial disconnection of the lactone C–O bond and the C-17–C-18 bond leads to the ‘southern’ and ‘northern’ fragments **i** and **ii** respectively. Simplification of the ‘northern’ fragment **ii** leads to the diene **iii**, and further disconnection of the C-26–C-27 bond provides a vinylic halide **v** and a propargylic alcohol **iv**. The latter can be obtained from a *trans* 2,5-disubstituted dihydrofuranone **vi** of a type generated by a highly diastereoselective metal-mediated reaction of the diazo ketone **vii**.<sup>8</sup> In the overall

synthetic plan, it is expected that dihydrofuranone **vi** will serve as a precursor to the C-1 to C-7 portion of the southern fragment **i**, allowing both key tetrahydrofuran-containing fragments to be prepared from a common intermediate.<sup>9</sup> A similar strategy was employed by Carter and Mahaparta in their very recent total synthesis of amphidinolide F.<sup>7</sup>

**Scheme 1.** Retrosynthetic Analysis of Amphidinolide C



The requisite dihydrofuranone was prepared from dimethyl D-malate (Scheme 2). Selective reduction of the α-hydroxy ester using the procedure by Saito et al. provided a diol,<sup>10</sup> the primary hydroxyl group of which was protected to give the TBS ether **6**. The remaining secondary hydroxyl group was then allylated using the acid-catalyzed reaction of an imidate to afford the allyl ether **7**.<sup>11</sup> Saponification of the ester provided the carboxylic acid **8**, and activation of this as a mixed anhydride followed by treatment with a solution of diazomethane gave the α-diazo ketone **9**. Treatment of this compound with Cu(acac)<sub>2</sub> in THF at reflux afforded the dihydrofuranone **10** as a single isomer in high yield.<sup>8</sup>

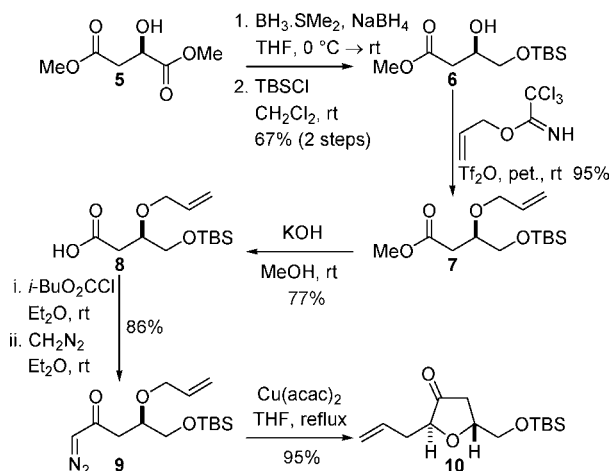
Following the synthesis of the ketone **10**, the first challenge was the deletion of the carbonyl group from the ring to provide the tetrahydrofuran corresponding to the C-18 to C-24 subunit of amphidinolide C. Initial attempts to perform removal of the ketone were undertaken by formation of a tosyl hydrazone followed by

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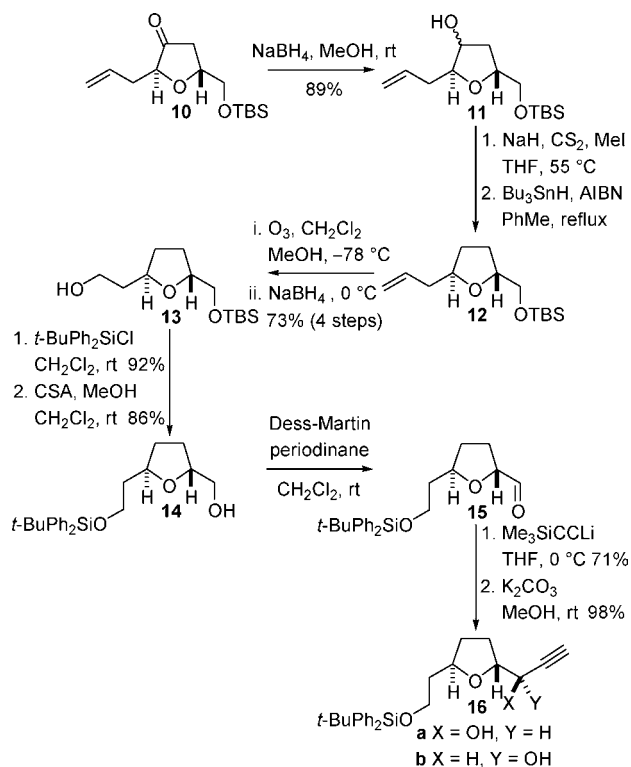
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**Scheme 2.** Synthesis of *trans*-Dihydrofuranone **10**

reduction.<sup>12</sup> However, this approach was unsuccessful and so the use of radical deoxygenation methods was explored (Scheme 3). The ketone **10** was reduced to a diastereomeric mixture of alcohols **11** that were then converted into the corresponding xanthate esters. Treatment of this mixture under Barton–McCombie conditions delivered the deoxygenated tetrahydrofuran **12**.<sup>13</sup> Ozonolysis and reduction then afforded the alcohol **13** in an overall yield of 73% over four steps, with minimal purification necessary. Protection of the primary alcohol as a *tert*-butyldiphenylsilyl ether followed by selective acid-catalyzed removal of the TBS group generated the alcohol **14**. Oxidation of the primary alcohol using the Dess–Martin protocol provided the aldehyde **15** required for the addition of an alkyne nucleophile.

Several sets of reaction conditions were examined in an effort to perform a stereoselective nucleophilic attack on the aldehyde **15**. Attempted reagent-controlled introduction of the alkyne using Carreira's alkynylation protocol<sup>14</sup> did not proceed efficiently. Efforts to achieve substrate control by using various alkyne nucleophiles and reaction conditions were not successful; a 1.5:1 mixture of the diastereomeric propargylic alcohols **16a** and **16b** was obtained from the reaction performed with magnesium trimethylsilylacetylide in THF at  $-78\text{ }^{\circ}\text{C}$ . Oxidation of the mixture of alcohols to the corresponding ynone proceeded in good yield, but attempted stereoselective ketone reduction using L-selectride or under Luche conditions at  $-78\text{ }^{\circ}\text{C}$  resulted in little stereocontrol (1:1 and 1.5:1 of **16a:16b**, respectively).

Following preparation of the propargylic alcohols **16a,b**, attention turned to the synthesis of the vinylic iodide coupling partner **19** (Scheme 4). Hexanal was

**Scheme 3.** Synthesis of Propargylic Alcohol **16**

methylenated under Mannich conditions,<sup>15</sup> and the resulting enal was subjected to the Grignard addition of TMS acetylene to provide a racemic mixture of propargylic alcohols **17**. Kinetic resolution was then performed using Sharpless asymmetric epoxidation, and the allylic alcohol (*S*)-**17** was obtained with 98% ee.<sup>16</sup> TBS protection of the secondary alcohol, removal of the TMS group, and subsection of the resulting terminal alkyne to modified Negishi carboalumination and iodination conditions<sup>17</sup> provided the unstable *E*-vinylic iodide **19** stereoselectively and in good yield.

Although it was possible to separate the diastereomeric alcohols **16a,b**, the mixture was used in the subsequent step. Coupling of the vinylic iodide **19** to a mixture of the propargylic alcohols **16a,b** under Sonogashira conditions was achieved in 82% yield (Scheme 5).<sup>18</sup> The propargylic alcohol functionality of the coupled products **20a,b** allowed stereoselective reduction of the alkyne to be achieved using Red-Al to give the desired *E*-configured alkenes **21a,b**.<sup>6i</sup> Oxidation of the diastereomeric mixture of allylic alcohols to give the enone was accomplished in quantitative yield using the Dess–Martin periodinane. A subsequent stereoselective Luche reduction of the dienone provided the alcohol **21a** corresponding to the entire C-18

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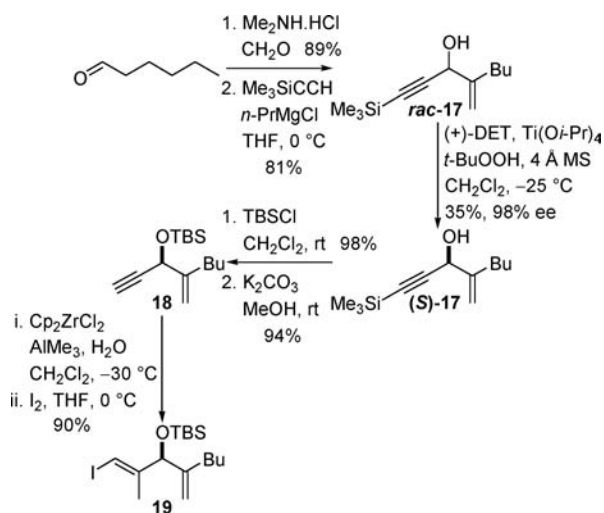
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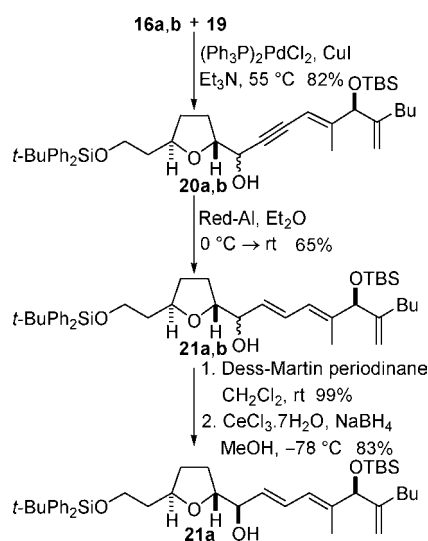
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**Scheme 4.** Stereoselective Synthesis of Vinylic Iodide **19**



**Scheme 5.** Completion of the C-18–C-34 Fragment of Amphidinolide C



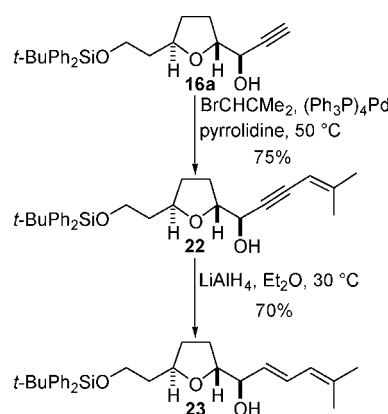
to C-34 fragment in 83% yield as a single stereoisomer through Felkin–Anh control.

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(20) Alcohol **16a** could be obtained as a single diastereomer by addition of lithium trimethylsilylacetylide to the aldehyde **15**, treatment of resulting diastereomeric alcohols with dicobalt octacarbonyl, chromatographic separation of the diastereomeric cobalt complexes, and oxidative removal of cobalt followed by desilylation (see Supporting Information for full details).

The power of the Sonogashira coupling reaction for the installation of a range of tail units was further illustrated by the construction of the C-18–C-29 fragment of amphidinolide F (Scheme 6). In this case, a copper-free variant of the Sonogashira reaction<sup>19</sup> was used to couple 1-bromo-2-methylpropene to the alkyne **16a**.<sup>20</sup> This modification to the procedure was required because significant homocoupling of the alkyne was encountered when the reaction was performed in the presence of copper iodide. When pyrrolidine was used as the solvent, clean coupling occurred to provide **22** in 75% yield. The propargylic alcohol was reduced to the corresponding *E*-allyl alcohol **23** in an analogous manner to the reduction of **20a,b** (Scheme 5).

**Scheme 6.** Completion of the C-18–C-29 Fragment of Amphidinolide F



In summary, we have synthesized the C-18–C-34 fragment of amphidinolide C and the C-18–C-29 fragment of amphidinolide F using routes in which diastereoselective rearrangement of the diazo ketone **9** is used to construct the key *trans*-2,5-disubstituted tetrahydrofuran. The entire ‘northern’ fragments **21a** and **23** were constructed from **16** using Sonogashira coupling reactions to install the side chains found in the natural products. Stereoselective enone reduction was used to control the stereochemistry at C-24 in the case of the C-18–C-34 fragment of amphidinolide C.

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**Supporting Information Available.** Experimental procedures and data for **7–23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.