## A Formal Synthesis of the C1–C9 Fragment of Amphidinolide C Employing the Tamaru Reaction

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Homoallylation of aldehydes with isoprene and triethylborane catalyzed by Ni(acac)<sub>2</sub> gave hydroxyalkenes in good yield with excellent regioand stereoselectivity. Cross metathesis of the hydroxyalkenes with methyl acrylate using second-generation Grubbs catalyst and copper(I) iodide afforded  $\alpha$ , $\beta$ -unsaturated esters, which underwent cyclization in the presence of DBU to produce tetrahydrofurans with the correct relative configuration for the C1–C9 fragment of amphidinolides C, C2, and F.

The symbiotic marine dinoflagellate *Amphidinium* sp., isolated from the cells of aceol flatworms *Amphiscolops* sp., produces a structurally diverse group of macrolide natural products.<sup>1</sup> This group of macrolides, named amphidinolides, contains over 30 compounds, and the majority of them possess some level of cytotoxicity.

Amphidinolide C (1) (Scheme 1), isolated from the Y-5 strain of *Amphidinium* sp., is one of the most cytotoxic members of the amphidinolide family.<sup>2</sup> Embedded within this macrolide are two 2,5-*trans* tetrahydrofuran rings and 12 stereocenters. Amphidinolide C was shown to possess cytotoxicity against murine lymphoma L1210 (IC<sub>50</sub> 0.0058  $\mu$ g/mL) and human epidermoid carcinoma KB (IC<sub>50</sub> 0.0046  $\mu$ g/mL) in vitro. Interestingly, amphidinolides C2 (**2**) and F (**3**), which vary only in the structure of the side chain, are close to 1000-fold less active.

Due to their unique structure and noteworthy biological activity, amphidinolides C (1), C2 (2), and F (3) have become

targets for synthesis. The syntheses of several fragments of these molecules have been reported, but they have yet to succumb to total synthesis.<sup>3</sup>

Our retrosynthetic analysis (Scheme 1) for amphidinolide C divides the molecule into four different subunits; the northern (C18–25), the southern (C1–C9), and the western (C10–C17) subunits and the side chain (C26–C34). In this paper, we describe the synthesis of the tetrahydrofuran (THF) ring of C1–C9 fragment of amphidinolides C, C2, and F.

The C1–C9 fragment of amphidinolide C contains a 2,3,5trisubstituted tetrahydrofuran with a methyl substituent at the 3-position (4-position in amphidinolide C numbering). The stereochemical relationship between the substituents is 2,5and 2,3-*trans* and 3,5-*cis*. Similar 3-methyl-substituted tetrahydrofuran moieties are found in several other natural products, e.g., monensin A,<sup>4</sup> amphidinolides T1<sup>5</sup> and T3,<sup>6</sup> tetronasin,<sup>7</sup> gambieric acid,<sup>8</sup> and gymnodimine.<sup>9</sup>

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Scheme 1. Retrosynthetic Analysis of Amphidinolide C



A particular challenge is finding a method to install the methyl group in an efficient manner. A retrosynthetic analysis (Scheme 2) reveals that unfolding of the tetrahydrofuran ring results in an unsaturated alcohol with a 1,3-*anti* relationship between the methyl and hydroxyl groups. In the forward sense, the tetrahydrofuran can be formed by the addition of



the alcohol across the double bond. The *cis* orientation of  $R^1$  and the methyl group in the transition state for cyclization would direct the developing stereocenter at position 2 *trans* relative to the existing stereocenters (positions 3 and 5), resulting in the required 2,5*-trans* tetrahydrofuran ring. Substituted 1,3*-anti* unsaturated alcohols can be prepared very efficiently from appropriately functionalized aldehydes using the highly diastereoselective nickel-catalyzed homoallylation chemistry reported by Tamaru et al.<sup>10</sup> Herein, we report the results of the Tamaru reaction with a series of novel electrophiles with specific application to the synthesis of the C1–C6 tetrahydrofuran fragment from amphidiolides C, C2, and F.

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The known homoallylation of benzaldehyde was used to initiate a model study. The reaction of benzaldehyde with isoprene catalyzed by Ni(acac)<sub>2</sub> and promoted by triethylborane yielded homoallyl alcohol **4** with a 1,3 *anti/syn* ratio of >15:1 (Scheme 3).<sup>10a</sup> Palladium-catalyzed cyclization/methoxycarbonylation of the hydroxyalkene **4** using modified Semmelhack conditions<sup>11</sup> gave the tetrahydrofuran **6** in 68% yield with a 2,5*-trans/cis* ratio of 9:1.



Alternatively, cross metathesis of the hydroxyalkene **4** with methyl acrylate in the presence of second-generation Grubbs catalyst and copper(I) iodide<sup>12</sup> gave the  $\alpha$ , $\beta$ -unsaturated methyl ester **5** in 79% yield. Cyclization of **5** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)<sup>13</sup> in CH<sub>2</sub>Cl<sub>2</sub> gave 2,5-*trans*-tetrahydrofuran **6** as a single diastereomer in an

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excellent 93% yield. Thus, using either method, the required 2,5-*trans*-tetrahydrofuran with correct relative configuration for the C1–C9 fragment of amphidinolide C was achieved.

The next challenge was to identify a suitable aldehyde that contained, or that had suitable functionality for introducing, the 1,2-*anti* diol found at positions 7 and 8 of ampidinolide C. Initial efforts focused on the hemiacetal derivatives of erythronolactone.

Homoallylation of the bis-*tert*-butyldimethylsilyl (TBS)protected hemiacetal **8** provided two diastereomers **9a** and **9b** in 63% combined yield with 1:6 diastereoselectivity (Scheme 4). The diastereomers were separated by silica gel column chromatography. The major diastereomer **9b** was crystalline and could be recrystallized to give X-ray quality crystals.



The crystal structure of major diastereomer **9b** (see the Supporting Information) clearly shows that the silyloxy groups at C2 and C3 are *anti* and the hydroxyl and methyl groups at C4 and C6 are *anti*. However, the silyloxy at C3 and the hydroxy at C4 have the wrong relative configuration (*anti*), and thus, the minor isomer **9a** has the correct relative (3,4-syn) and absolute configuration required for amphidinolide C.

The observed diastereofacial selectivity was much higher than expected for the homoallylation reaction. In the limited number of chiral aldehydes investigated by Tamaru et al., the diastereofacial selectivity with respect to the aldehyde was typically very low (1:1 to 1.6:1).<sup>10c</sup> The formation of the major isomer **9b** appears to follow the trend observed by Evans et al. in the aldol reactions of a series of alkoxy and bisalkoxy aldehydes.<sup>14</sup> A Cornforth model<sup>15</sup> was used to explain stereochemical outcome of the addition of the enolate to the aldehyde.

Undaunted by this setback, the cyclization of both diastereomers 9 was investigated. The Semmelhack palladium-

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catalyzed cyclization/methoxycarbonylation of major isomer **9b** failed to yield the tetrahydrofuran **14b**. Therefore, the alternate chain extension and cyclization method was examined. Cross-metathesis of both the minor isomer **9a** and the major isomer **9b** with methyl acrylate gave  $\alpha$ , $\beta$ -unsaturated methyl esters **13a** and **13b**, respectively (Scheme 5). Cyclization





of **13a** and **13b** using DBU afforded the tetrahydrofurans **14a** and **14b**. Some migration of silyl group was observed during the cyclization process. The TBS group migrated from the secondary **14** to the primary position **15** (Scheme 5).<sup>16</sup>

In order to avoid protecting group migration and perhaps effect a more favorable stereochemical outcome, an alternate protecting group was examined. Homoallylation of acetonideprotected hemiacetal **11** (Scheme 4) gave a mixture of diastereomers **12a** and **12b** in a 1:3 ratio. The diastereomers were separable by repeated silica gel column chromatography. Cross metathesis of the major diastereomer **12b** with methyl acrylate (Scheme 6) followed by cyclization with DBU gave **17** in 80% yield.





To compare the configuration of the tetrahydrofurans 17 and 14b obtained from the acetonide-protected hemiacetal 11 and the TBS-protected hemiacetal 8, the protecting groups were removed (Scheme 7). The TBS groups were cleaved using HF/pyridine in MeOH, which provided the triol 18 in

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70% yield. The acetonide group was removed using Amberlyst 15 resin in MeOH to give the triol **18** in 60% yield. The <sup>1</sup>H and <sup>13</sup>C spectra of the triol **18** obtained by deprotection of both **14b** and **17** were identical, suggesting that the tetrahydrofuran obtained from both hemiacetals have the same configuration.



Next, our attention turned to epoxy aldehydes. Epoxides are versatile functional groups that can be opened with water to reveal a diol or oxidatively cleaved to obtain an aldehyde. As a consequence, epoxycinnamaldehyde **19** was selected as the next substrate for homoallylation. Oxidation of commercially available (2R,3R)-3-phenylglycidol (epoxycinnamyl alcohol)<sup>17</sup> gave (2R,3R)-3-phenylglycidal **19** in 73% yield. Homoallylation of **19** gave a separable mixture of diastereomers **20** in a 2.5:1 ratio and 63% combined yield (Scheme 8). The absolute configuration of the diastereomers was determined by the Mosher ester method.<sup>18</sup> The major isomer **20a** possessed the correct configuration for the tetrahydrofuran ring of amphidinolide C.

Cross metathesis of **20a** with methyl acrylate (or ethyl acrylate) gave  $\alpha,\beta$ -unsaturated methyl (or ethyl) ester **21a** (or **21b**) which on cyclization with DBU gave **22a** (or **22b**) as a single isomer. Cleavage of the epoxide in tetrahydrofuran **22a** (or **22b**) with NaIO<sub>4</sub> in acetonitrile/water (2:1)<sup>19</sup> gave aldehyde **23a** (or **23b**), which could be isolated or subsequently reduced in situ with NaBH<sub>4</sub> in MeOH to afford alcohol **24a** (or **24b**) in 64% overall yield (Scheme 8). The enantiomers of alcohol **24a** could be separated by GC on a chiral stationary phase. The alcohol (**24a**) derived from the nonracemic glycidol had an enantiomeric excess of >95%. The tetrahydrofuran aldehyde **23b** and alcohol **24b** had <sup>1</sup>H and <sup>13</sup>C NMR spectra and optical rotation matching those reported by Roush and co-workers.<sup>3a</sup>

Scheme 8. Homoallylation, Cross Metathesis, and Cyclization



Aldehyde **23b** has been elaborated into the C1–C9 fragment of amphidinolide C by Roush and co-workers.<sup>3a</sup> Therefore, the synthesis of tetrahydrofuran alcohol **24b** and aldehyde **23b** constitute a formal synthesis of the C1–C9 fragment of amphidinolide C. The aldehyde **23b** was prepared in five steps from the commercially available phenyl glycidol in 12% overall yield. Roush reported two routes to C1–C9 fragments. The first approach gave a C1–C9 fragment in 13 steps in <7% yield (17 from commercial materials). A second more efficient approach proceeded via aldehyde **23b**, which was formed in 10 steps from commercial materials in 21% overall yield. We have provided a shorter synthesis of **23b**, but with a lower overall yield.

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**Supporting Information Available:** Detailed experimental procedure and spectral data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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