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

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Abstract

Homoallylation of aldehydes with isoprene and triethyl borane, catalyzed by $\text{Ni}(\text{acac})_2$ gave hydroxy alkenes in good yield with excellent regio- and stereoselectivity. Cross metathesis of the hydroxy alkenes with methyl acrylate using second generation Grubbs catalyst and copper(I) iodide afforded α,β -unsaturated esters, which underwent cyclization in the presence of DBU to produce tetrahydrofurans with the correct relative configuration for C1-C9 fragment of amphidinolide 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.¹ 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.² 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_{50} 0.0058 $\mu\text{g/mL}$) and human epidermoid carcinoma KB (IC_{50} 0.0046 $\mu\text{g/mL}$) *in vitro*. Interestingly, amphidinolide C2 (**2**) and F (**3**), which vary only in the structure of the side chain, are close to a thousand 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.³

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 report, we describe the synthesis of the tetrahydrofuran (thf) ring of C1-C9 fragment of amphidinolide C, C2 and F.

The C1-C9 fragment of amphidinolide C contains a 2,3,5 trisubstituted tetrahydrofuran with a methyl substituent at the 3 position (4 position in amphidinolide C numbering). The stereochemical relationship between the substituents is 2,5- and 2,3-*trans* and 3,5-*cis*.

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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>.

Similar 3-methyl substituted tetrahydrofuran moieties are found in several other natural products, e.g. monensin A,⁴ amphidinolide T15 and T3,⁶ tetronasin,⁷ gambieric acid⁸ and gymnodimine⁹.

A particular challenge is finding an efficient 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 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 R¹ 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.*¹⁰ 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 amphidiolide C, C2 and F.

The known homoallylation of benzaldehyde was used to initiate a model study. The reaction of benzaldehyde with isoprene catalyzed by Ni(acac)₂ and promoted by triethyl borane yielded homoallyl alcohol **4** with 1,3 *anti* to *syn* ratio >15:1 (Scheme 3).^{10a} Palladium catalyzed cyclization/methoxycarbonylation of the hydroxy alkene **4** using modified Semmelhack conditions¹¹ gave the tetrahydrofuran **6** in 68% yield with 2,5-*trans* to *cis* ratio 9:1.

Alternatively, cross metathesis of the hydroxy alkene **4** with methyl acrylate in the presence of second generation Grubbs catalyst and copper(I) iodide¹² gave the α,β -unsaturated methyl ester **5** in 79% yield. Cyclization of **5** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)¹³ in CH₂Cl₂ gave 2,5-*trans*-tetrahydrofuran **6** as a single diastereomer in an 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 amphidinolide 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 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).^{10c} 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.¹⁴ A Cornforth model¹⁵ 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-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 α,β -unsaturated methyl ester **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).¹⁶

In order to avoid protecting group migration and perhaps effect a more favorable stereochemical outcome, an alternate protecting group was examined. Homoallylation of acetonide protected 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 70% yield. The acetonide group was removed using Amberlyst 15 resin in MeOH to give the triol **18** in 60% yield. The ¹H and ¹³C 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 (2*R*,3*R*)-3-phenylglycidol (epoxycinnamyl alcohol)¹⁷ gave (2*R*,3*R*)-3-phenylglycidol **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's ester method.¹⁸ 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 α,β -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 NaIO₄ in acetonitrile/water (2:1)¹⁹ gave aldehyde **23a** (or **23b**) which could be isolated or subsequently reduced *in situ* with NaBH₄ 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 ¹H and ¹³C NMR spectra and optical rotation matching those reported by Roush and coworkers.^{3a}

Aldehyde **23b** has been elaborated into the C1-C9 fragment of amphidinolide C by Roush and coworkers.^{3a} 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 5 steps from the commercially available phenyl glycidol in 12% overall yield. Roush reported two routes to **23b**. The first approach gave **23b** in 13 steps in <7% yield (17 from commercial materials) and the second approach gave **23b** in 10 from commercial materials in 21% overall yield. We have provided a shorter synthesis, but with a lower overall yield.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Retrosynthetic analysis of amphidinolide C

Scheme 2.
Retrosynthetic analysis of the C1-C9 fragment

Scheme 3.
Synthesis of tetrahydrofuran ring

Scheme 4.
Homoallylation of erythrolactol

Scheme 5.
Cross metathesis and cyclization

Scheme 6.
Cross metathesis and cyclization

Scheme 7.
Deprotection of TBS and acetonide groups

Scheme 8.
Homoallylation, cross metathesis and cyclization