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Synthesis of the C-1—C-17 Fragment of Amphidinolides C, C2, C3, and F

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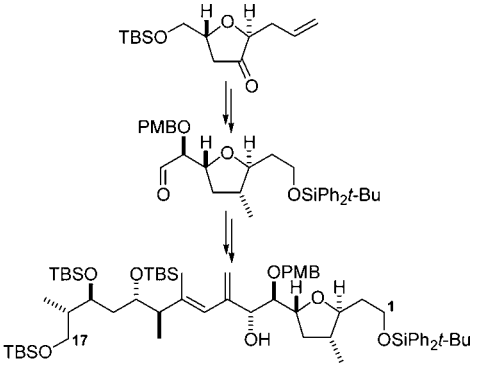
ABSTRACT



The C-1—C-17 fragment of amphidinolides C, C2, C3, and F has been constructed from a *trans*-2,5-disubstituted dihydrofuranone prepared by diastereoselective rearrangement of a free or metal-bound oxonium ylide generated from a metal carbenoid. The dihydrofuranone was converted into an aldehyde corresponding to the C-1—C-8 framework, and this was coupled to the C-9—C-17 unit by nucleophilic addition of a vinylic anion.

Amphidinolides C, C2, C3, and F are structurally related members of a large family of marine natural products isolated from microalgae of *amphidinium* sp. (Figure 1). Amphidinolide C possesses substantial anticancer activity (IC_{50} values < 0.01 μg mL^{-1} against certain cell lines).[1]

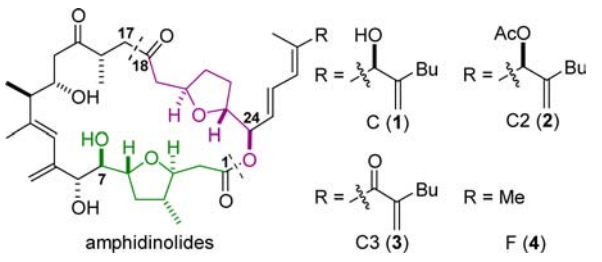


Figure 1. Amphidinolides C, C2, C3, and F.

The unique structures and bioactivities of amphidinolides C,[2] C2,[3] C3,[4] and F[5] have aroused significant interest in their syntheses, and several groups have reported syntheses of fragments of the compounds.[6] Very recently, Carter and Mahapatra completed a synthesis of amphidinolide F in which a common intermediate was used to prepare both tetrahydrofurans.[7]

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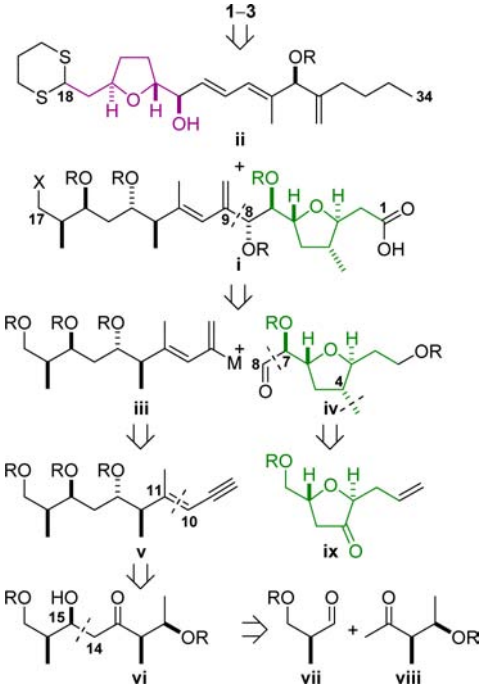
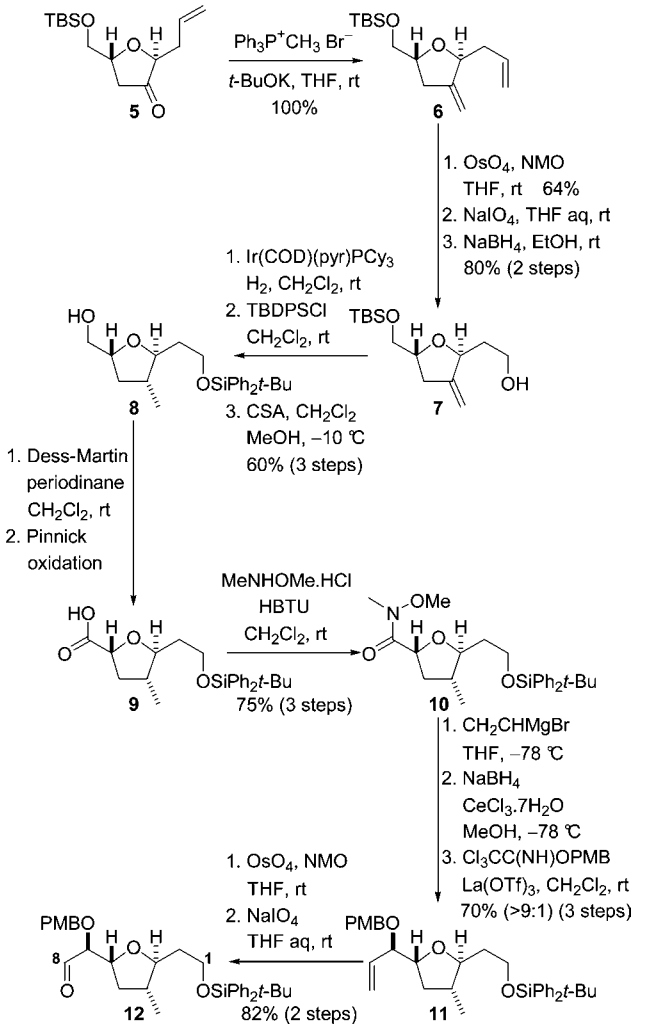
The macrolactone common to amphidinolides C, C2, C3, and F (**1**−**4**, Figure 1) contains two *trans*-2,5-disubstituted tetrahydrofurans. The similarity of the rings inspired us to design a synthesis in which a readily accessible dihydrofuranone bearing suitable functionality would serve as a common intermediate for the construction of two acyclic fragments of similar size and complexity, thus laying the foundations for convergent and efficient total syntheses of all four natural products. This approach has been validated recently by Mahapatra and Carter who completed their total synthesis of amphidinolide F from a common tetrahydrofuranyl intermediate.[7]

Scheme 1. Retrosynthetic Analysis of Amphidinolide C



The retrosynthetic analysis of amphidinolide C is shown in Scheme 1. As described in the preceding paper,[8] initial disconnection of the lactone C−O bond and the C-17−C-18 bond gives the 'northern' and 'southern' fragments **ii** and **i**. Disconnection of the 'southern' fragment **i** through the C-8−C-9 bond leads to the vinylic organometallic compound **iii** and the aldehyde **iv**. The vinylic organometallic compound **iii** can be converted into the enyne **v**, implying regioselective hydrometalation of the alkyne in the forward direction. Disconnection through the C-10−C-11 alkene and oxidation at C-13 then reveals the β-hydroxy ketone **vi**. Subsequent aldol disconnection between C-14 and C-15 leads to the aldehyde **vii** and the ketone **viii**, both of which can be prepared from chiral pool materials. The aldehyde **iv** can undergo two one-carbon disconnections to give the ketone **ix** which corresponds to the intermediate used in our synthesis of the 'northern' fragment.[8] Consequently, the intermediate prepared by diastereoselective rearrangement of a free or metal-bound oxonium ylide, generated by intramolecular cyclization of a copper carbenoid,[9] will be used for the preparation of both the 'northern' and 'southern' fragments **ii** and **i**.

Scheme 2. Construction of the C-1−C-8 Fragment



The dihydrofuranone **5** corresponding to the C-1−C-7 fragment was prepared from dimethyl D-malate in six steps as described in the preceding paper.[8] Wittig methylenation of the ketone **5** proceeded to afford diene **6** in quantitative yield (Scheme 2). Selective dihydroxylation of the

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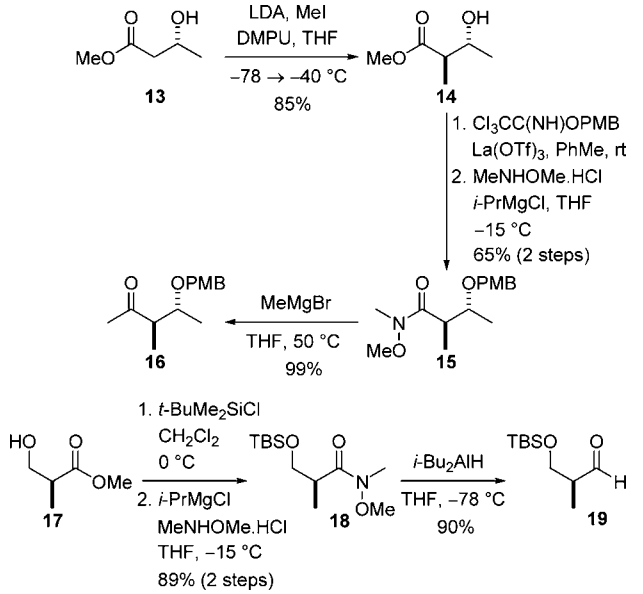
side-chain alkene was achieved in 64% yield, and the resulting diol was then subjected to oxidative cleavage. The intermediate aldehyde was reduced with $NaBH_4$ to provide the alcohol **7**, which was to be subjected to hydrogenation of the methylene group to install the C-4 methyl substituent. The use of homogeneous catalysts to control the stereochemical outcome hydrogenation reactions through reversible coordination to hydroxyl or carbonyl groups is precedented,[10] and gratifyingly this approach proved to be successful in our case. Hydrogenation of the alkene **7** using Crabtree's catalyst (12 mol %) afforded the saturated product as a single isomer, and this compound was then converted into the alcohol **8** in good yield by silylation of the hydroxyl group with *tert*-butyldiphenylsilyl chloride and subsequent cleavage of the TBS ether.

The carboxylic acid **9** was prepared from the alcohol **8** by sequential Dess-Martin and Pinnick oxidation reactions. Subsequent HBTU-mediated coupling of the carboxylic acid **9** to *N*,*O*-dimethylhydroxylamine afforded the Weinreb amide **10**. Treatment of this amide with vinylmagnesium bromide resulted in the formation of the corresponding enone. An alternative synthesis of the enone by sequential oxidation of alcohol **8** to the aldehyde, addition of vinylmagnesium bromide, and oxidation of the resulting diastereomeric mixture of alcohols afforded material that was difficult to purify in 53% yield. A Luche reduction of the enone resulted in the clean formation of the required diastereomer (*dr* > 9:1) and was followed by PMB protection of the allylic alcohol by a Lewis acid catalyzed reaction with a trichloroacetimidate.[11] Construction of the aldehyde **12**, which corresponds to the C-1–C-8 fragment, was completed by dihydroxylation of the alkene followed by oxidative cleavage of the 1,2-diol.

Scheme 3. Synthesis of Ketone **16** and Aldehyde **19**



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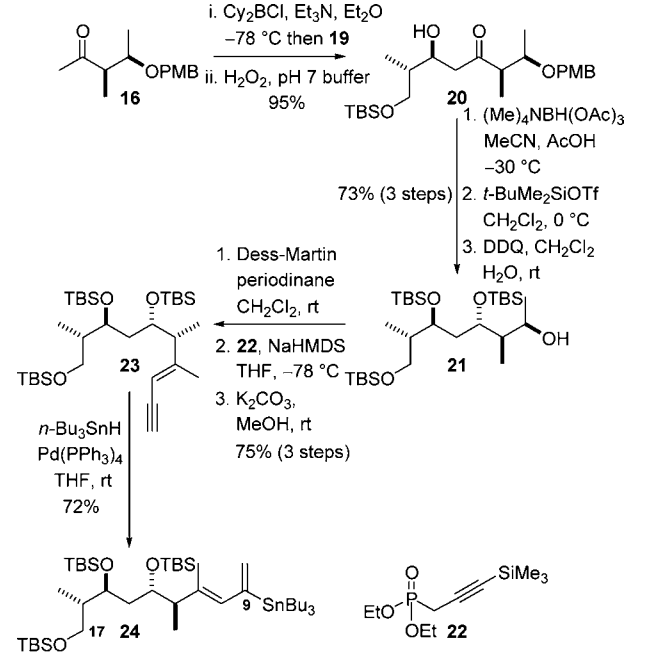
Synthesis of the C-9–C-17 fragment began with construction of the fragments shown in Scheme 3. The commercially available ester **13** was first α-methylated stereoselectively (*dr* > 10:1) and in high yield.[12] The hydroxyl group of the resulting *β*-hydroxy ester **14** was then protected, and the ester was converted into the Weinreb amide **15**.[13] Transformation of the amide into the target methyl ketone **16** was accomplished cleanly and in high yield by reaction of the amide **15** with methylmagnesium bromide. Aldehyde **19**, the requisite aldol coupling partner, was prepared from the Roche ester **17**. Protection of the hydroxyl group as a TBS ether was followed by conversion of the ester into the Weinreb amide **18**. Reduction of the Weinreb amide with DIBAL-H at low temperature afforded the aldehyde **19**.

Aldol condensation of the aldehyde **19** with the boron enolate generated from the methyl ketone **16** proceeded in excellent yield and afforded the *β*-hydroxy ketone **20** as a single diastereoisomer (Scheme 4), presumably as a consequence of reinforcing 1,4- and 1,5-stereoinduction.[14] Stereoselective directed ketone reduction with tetramethylammonium triacetoxyborohydride afforded the *anti*-1,3-diol with a high level of diastereocontrol (*dr* > 25:1).[15] Silylation of both hydroxyl groups was accomplished by treatment of the diol with *tert*-butyldimethylsilyl triflate, and the PMB ether was cleaved with DDQ under standard conditions. Oxidation of the resulting secondary alcohol **21** afforded the corresponding methyl ketone, and this was subjected to Horner–Wadsworth–Emmons olefination with phosphonate **22** (*E*/*Z* > 15:1).[16] Removal of the trimethylsilyl group with potassium carbonate in wet methanol afforded the terminal alkyne **23**, and subsequent palladium-catalyzed hydrostanylation with tributyltin hydride afforded the vinylic stannane **24** in good yield.[17]

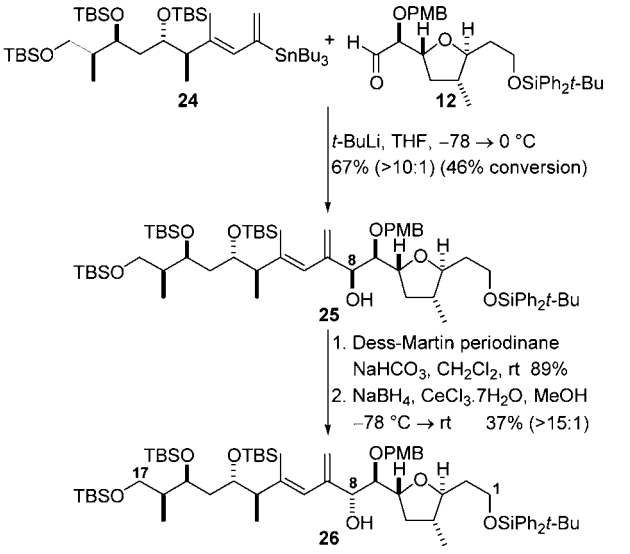
Scheme 4. Construction of the C-9–C-17 Fragment



Fragment coupling to complete the entire C-1−C-17 fragment was performed as shown in Scheme 5. Subjection of the vinyl stannane **24** to tin−lithium exchange and addition of the lithiated intermediate to the aldehyde **12** afforded the alcohol **25** with high diastereoselectivity (*dr* > 10:1). The configuration of the newly created stereogenic center at C-8 was assigned as *S* based on comparison of NMR data with those of closely related compounds prepared by Carter and Mahapatra during their recently reported total synthesis of amphidinolide F.[7,18] Thus, it was clear that the diastereomer of the required alcohol had been obtained and inversion of configuration at the C-8 stereogenic center was required. Oxidation of the alcohol with the Dess-Martin periodinane afforded the corresponding enone, and highly diastereoselective 1,2-reduction of the carbonyl group under Luche conditions afforded the alcohol **26** (*dr* > 15:1) with the required *R* configuration at the C-8 stereogenic center. The stereochemical outcome of the ketone reduction reaction was confirmed by comparison of the ^{1}H and ^{13}C NMR data obtained for the diastereomeric alcohols **25** and **26** with those of the closely related compound (C-1−C-14 fragment) prepared by Mahapatra and Carter.[7,18]

In summary, the C-1−C-17 fragment of amphidinolide C has been prepared in an efficient and stereoselective fashion. An important feature of this synthesis is the use of dihydrofuranone **5**, a starting material from which the carbon frameworks of both 'northern' and 'southern' fragments of the natural products have been synthesized. Other key transformations include stereoselective boron-mediated aldol condensation between the chiral pool derived fragments **16** and **19** to produce the C-1−C-9 unit, regioselective hydrostannylation of the enyne **23**, and tin−lithium exchange of the stannane **24** followed by nucleophilic addition to aldehyde **12**.

Scheme 5. Coupling to Complete the C-1−C-17 Fragment



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Supporting Information Available. Experimental procedures and data for **6**−**12**, **14**−**16**, **18**−**21**, and **23**−**26**, plus intermediate compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(18) For tabulated selected NMR data, see Supporting Information.
(19) Luche reduction of the enone prepared from the alcohol **25** was very slow, and some decomposition occurred. The yield of 37% is unoptimized.