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Synthesis of the C11–C29 Fragment of Amphidinolide F

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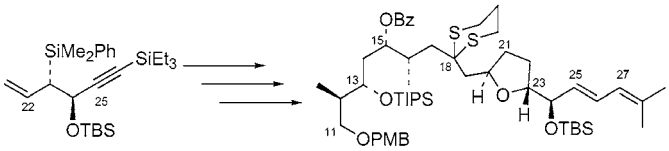
ABSTRACT



C11-C29 fragment (31) of amphidinolide F

An efficient synthesis of the C(11)–C(29) fragment 31 of amphidinolide F has been accomplished via a diastereoselective [3 + 2]-annulation reaction of allylsilane 5 and ethyl glyoxylate to prepare the key tetrahydrofuran 15 and a highly stereoselective methyl ketone aldol reaction to generate the C(11)–C(16) segment.

The amphidinolides are a structurally diverse group of bioactive secondary metabolites isolated from the symbiotic marine dinoflagellate *Amphidinium* sp. Kobayashi and coworkers have published numerous spectroscopic and semisynthetic studies relating to various members of this class, culminating in relative and/or absolute stereochemical assignments for most members of the amphidinolide family.[1] Importantly, Kobayashi has also demonstrated that many amphidinolides possess extremely potent antineoplastic activity.[1] The combination of structural diversity and potent cytotoxicity has led to interest in both the biosynthesis and mode(s) of action of these compounds. Accordingly, total syntheses of various members of this class (amphidinolides A,[2] K,[3] P,[4] J,[5] R,[6] T1,[7] T2−T5,[7a,c] and W[8]) have been reported, several resulting in reassignments in relative and/or absolute configuration for certain members of the family.[2d,3,4,8]

The 25-membered macrocycle possessing two embedded *trans*-tetrahydrofuran moieties is unique to amphidinolides F[9] (**1**) and C[10] (**2**) (Figure 1). While amphidinolide C (**2**) possesses potent cytotoxic activity against murine lymphoma L1210 and epidermoid carcinoma KB cells in vitro (IC_{50} = 0.0058 and 0.0046 μg mL^{-1}, respectively), amphidinolide F displays much more modest activity (1.5 and 3.2 μg mL^{-1}, respectively).[9,10] Kobayashi has reported partial syntheses of the C(19)−C(26) and C(1)−C(8) portions of **1** and **2** in connection with stereochemical assignments.[11] We report herein our synthetic studies on **1** and **2**, resulting in the synthesis of the C11−C29 fragment **31** corresponding to amphidinolide F (**1**).

A retrosynthetic analysis of **1** and **2** is presented in Figure 1. A variety of metal-mediated processes could allow the late-stage union of functionalized tetrahydrofurans **3** and **4**.

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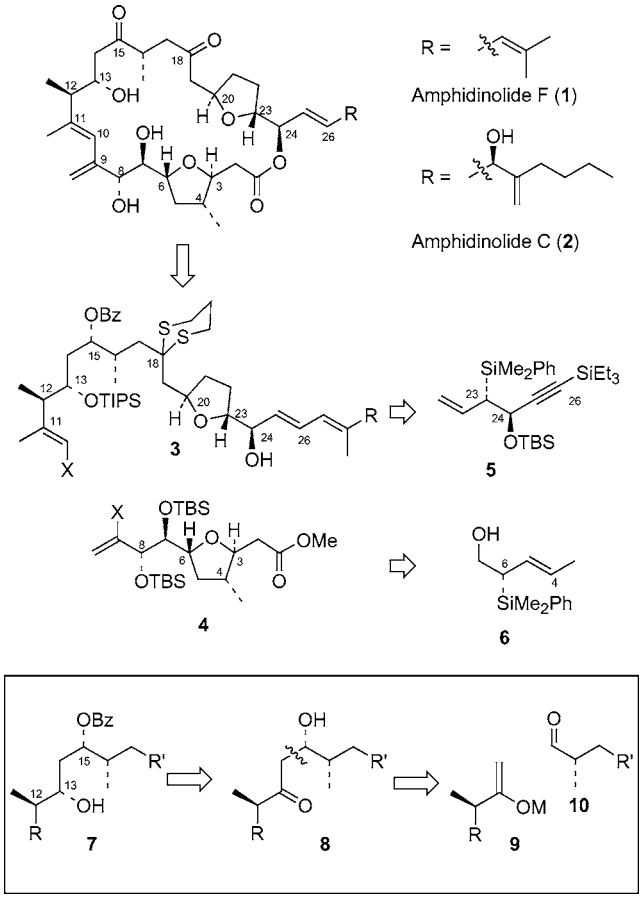
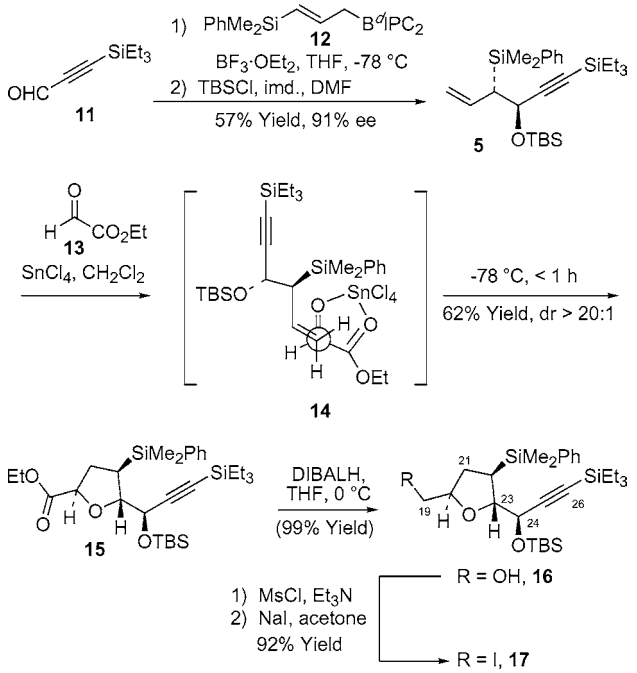


Figure 1. Retrosynthetic analysis.

Of current interest to our laboratory is the convergent synthesis of substituted tetrahydrofurans via the stereocontrolled [3 + 2]-annulation of aldehydes and allylsilanes.[12] Accordingly, we anticipated that the C(20)−C(23) and C(3)−C(6) tetrahydrofuran units of **3** and **4** would be constructed via chelate-controlled [3 + 2]-annulations of chiral allylic silanes **5** and **6**.[13] Further examination of **1** and **2** reveals the opportunity for formation of the C(13)−C(14) bond via a methyl ketone aldol reaction (Figure 1). To achieve Felkin-type selectivity in the aldol step, replacement of the C(15) ketone with a (*S*)-hydroxyl group (as in **3** and **7**) reveals a 1,3-diol that could derive from *β*-hydroxy ketone **8**. In the forward sense, intermediate **8** could result from a matched double-asymmetric aldol reaction (i.e., **9** + **10** → **8**).[14] Stereochemical information could then be effectively relayed to C(13) in **7** via an Evans−Tishchenko reduction.[15]

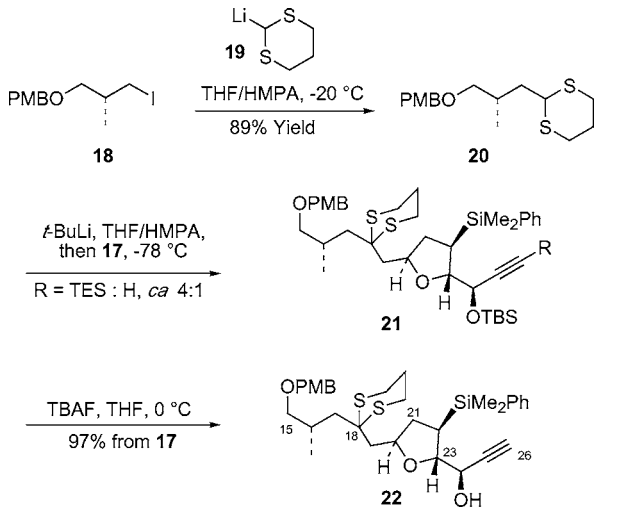
Efforts toward the key C(20)−C(23) tetrahydrofuran began with known aldehyde **11**.[16] Silylallylboration of **11** with (+)-pinene-derived silylallylborane **12**[17] followed by TBS-protection afforded α-hydroxylallylsilane **5** in 57% overall yield (91% ee). Treatment of **5** with ethyl glyoxylate (**13**) and $SnCl_4$ gave [3 + 2]-annulation adduct **15** (consistent with *syn*-synclinal transition state **14**)[12c] in 62% yield as a single diastereomer.[18] Subsequent standard manipulations of **15** provided iodide **17** in excellent yield.

Scheme 1. Synthesis of the C(20)−C(23) Tetrahydrofuran



Studies of the eventual protiodesilylation reaction that would be used to excise the $PhMe_2Si-$ substituent of **15**−**17** revealed that a dithiane carbonyl protecting group would survive the harsh basic reaction conditions anticipated for the C(sp^3)−$SiMe_2Ph$ bond cleavage (vida infra).[19] Accordingly, alkylation of iodide **17** with dithiane **20**[20] (Scheme 2) afforded **21** as a mixture of silylated and desilylated

Scheme 2. Preparation of Propargyl Alcohol **22**

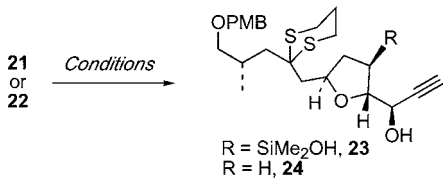


terminal alkynes (i.e., R = TES and H, ca. 4:1). Subsequent exposure of the crude reaction mixture to tetrabutylammonium fluoride in THF at 0 °C gave propargyl alcohol **22** in 97% yield from iodide **17**.

Allyl- and crotylsilanes have proven to be powerful intermediates for the convergent preparation of stereodefined

tetrahydrofurans, as illustrated in the present work for the rapid construction of the C(20)−C(23) tetrahydrofuran moiety of amphidinolides C/F. However, this method necessarily generates tetrahydrofurans with silicon substitution on the newly formed tetrahydrofuran ring. In the current case, where an unsubstituted tetrahydrofuran is required, a subsequent protiodesilylation step is used to remove the dimethylphenylsilyl substituent. Early efforts on the protiodesilylation reaction of C(sp^3)−$SiMe_2Ph$ units in our laboratory[12c,21] made use of a modified Hudrlik reaction,[22] in which TBAF was added to Hudrlik's standard conditions for this reaction (5% KO^{t}Bu, 18-crown-6, DMSO−H_2O, 95 °C) to effect in situ deprotection of the proximal TBS ether to give the free hydroxyl group, which was believed to be required for the subsequent protiodesilylation step.[22] Unfortunately, application of this protocol to **21** or **22** proved to be quite problematic, requiring rigorous degassing and extended reaction times to generate protiodesilylated adduct **24** in low yield (entry 1, Table 1). Prolonged exposure of **20** to these protiodesilylation conditions led to no appreciable decomposition, suggesting the propargylic alcohol unit in **21** and **22** was the offending functionality.

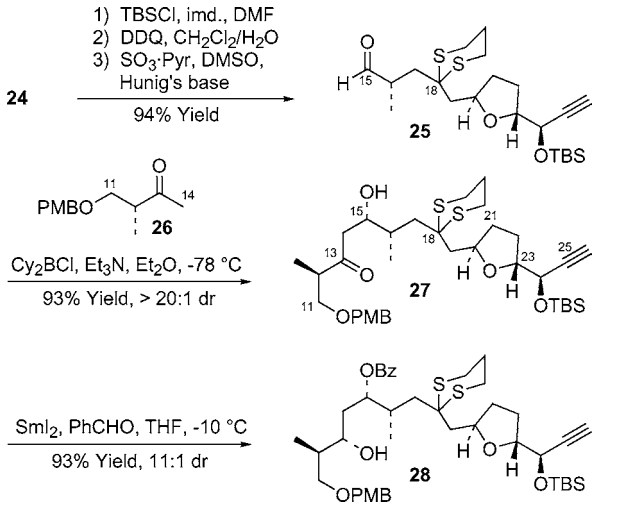
Table 1. Optimization of a C(sp^3)−$SiMe_2Ph$ Protiodesilylation



conditions	substrate	isolated yield (%) 22	23	24
(1) 5% KO^{t}Bu, DMSO/H_2O, 95 °C, 3 days, 18-crown-6, TBAF	**21** or **23**			<30
(2) 5% KO^{t}Bu, DMSO/H_2O, 95 °C, TBAF, 4 h	**21**		92	
(3) TBAF, THF/DMF, 85 °C, 4 h	**22**		56	35
(4) TBAF, THF/DMF, 85 °C, 24 h	**22**		<5	90
(5) Bu_4NOH, THF/DMF, 85 °C, 36 h	**22**	80		

During the course of efforts to optimize this experiment, we discovered that intermediate silanol **23** was generated rapidly and in good yield upon exclusion of 18-crown-6 from the reaction mixture (entry 2, Table 1).[23] Additionally, it was found that **23** converted to **24** upon exposure to standard conditions with added 18-crown-6 (cf. entry 1, Table 1). Hypothesizing that the conversion of silanol **23** to protiodesilylated **24** might proceed via the intermediacy of the corresponding siloxane, we treated **22** with TBAF in DMF, conditions known to effect the protiodesilylation of isolated siloxanes[24] (entries 3 and 4, Table 1). Under optimal conditions (entry 4), **24** was obtained in 90% yield from **22**. This result indicates that the "naked" alkoxides presumably generated upon treatment of **21**/**22** with 18-crown-6/KO^{t}Bu mixtures are *not* required for the efficient protiodesilylation of C(sp^3)−$SiMe_2Ph$ bonds (entry 4, Table 1). The TBAF-mediated protiodesilylation of **22** proceeds via the intermediacy of isolable silanol **23** (entry 3, Table 1) in THF/DMF solvent mixtures in excellent isolated yield.[25] With efficient access to the protiodesilylated C(15)−C(26) fragment **24** secured, we next focused on the stereoselective formation of the C(11)−C(16) polyketide segment of amphidinolides C/F. Protection of the C(24) hydroxyl as the corresponding TBS ether, DDQ-mediated deprotection of the −OPMB protecting group,[26] and Parikh−Doering oxidation[27] of the derived primary alcohol afforded aldehyde **25** in excellent

Scheme 3. Synthesis of β-Hydroxyketone **27**



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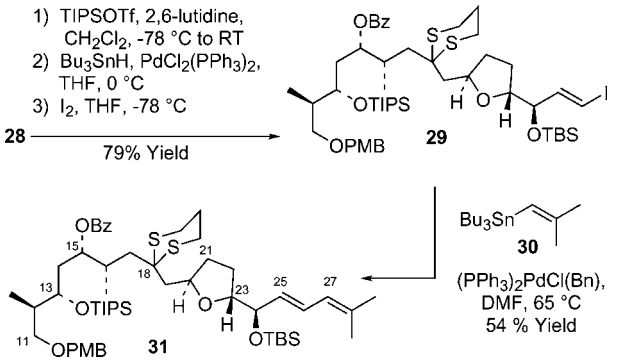
yield (94%, three steps). Treatment of aldehyde **25** with the dicyclohexylboron enolate derived from known methyl ketone **26**[28] afforded β-hydroxy ketone **27** as a single diastereomer in excellent yield (93%). The stereochemistry of the C(15)−OH group of aldol **27** was assigned by using the modified Mosher method,[29] which revealed the (*S*)-configuration at this center. This stereochemistry is fully consistent with the anticipated Felkin addition in the aldol step. Evans−Tishchenko reduction of β-hydroxy ketone **27** afforded an 11:1 mixture of diastereomers with *anti*-1,3-benzoate **28** predominating.[30]

Silylation of **28** followed by a two-step stannylation−iododestannylation sequence[31] afforded (*E*)-vinyl iodide **29**. This intermediate (**29**) represents a key point of divergence for the synthesis of a variety of amphidinolide C/F C(25) side-chain analogues from a common precursor. For example, Stille cross-coupling[32] with known vinylstannane **30**[33] afforded diene **31**, corresponding to the full amphidinolide F C(11)−C(29) fragment. Stille-coupling with a variety of other vinylstannanes could give rise to intermediates suitable for advancement to amphidinolide C (**2**) or any of a variety of nonnatural amphidinolide C/F congeners.

In summary, the C(11)−C(29) fragment (**31**) (18 steps, 9.7% overall yield from **11**) of amphidinolide F (**1**) has been synthesized via vinyl iodide **29**. Intermediate **29** (17 steps, 18% overall yield from **11**) should also be suitable for advancement to amphidinolide C (**2**). Generation of the

Scheme 4. Completion of the C(11)−C(29) Fragment **31**



C(20)−C(23) tetrahydrofuran fragment of **29** was accomplished via the chelation controlled [3 + 2]-annulation reaction of allylsilane **5** and ethyl glyoxylate, which provided **15** with excellent stereochemical control. Additionally, the C(11)−C(16) polyketide region has been stereoselectively synthesized via the highly selective aldol reaction of aldehyde **25** with the dicyclohexylboron enolate derived from methyl ketone **26**. Continued advancement of these intermediates toward the eventual total syntheses of **1** and **2** will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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