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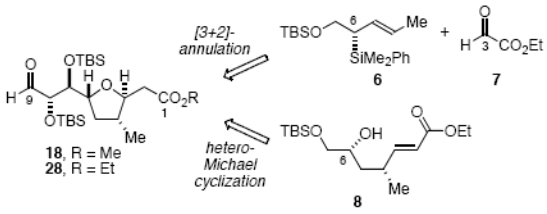
Stereoselective Syntheses of the C(1)-C(9) Fragment of Amphidinolide C

Robert H. Bates[a], **J. Brad Shotwell**[b], and **William R. Roush**[*,a,b]

a*Department of Chemistry, Scripps Florida, Jupiter, Florida 33458*

b*Department of Chemistry, University of Michigan, Ann Arbor, Michigan 41809*

Abstract



Stereoselective syntheses of the C(1)-C(9) fragments 18 and 28 of amphidinolide C have been developed. The first generation sequence involves a diastereoselective chelate-controlled [3 + 2]-annulation reaction of 6 and 7, while the second generation synthesis involves an intramolecular hetero-Michael cyclization of 8.

The amphidinolides are a structurally diverse group of natural products isolated from the symbiotic marine dinoflagellate *Amphidinium* sp. Kobayashi and coworkers have characterized more than 30 members of this family since 1986, many of which exhibit potent cytotoxicitity against human cancer cell lines.[1] Not surprisingly, the amphidinolides have attracted considerable interest from the synthetic community. Total syntheses of many members of this class have been reported, with several resulting in stereochemical reassigments.[2]

Amphidinolide C[3] (**1**) is one of the most cytotoxic members of this family, exhibiting in vitro cytotoxicities of 0.0058 and 0.0046 μg/mL against murine lymphoma L1210 and epidermoid carcinoma KB cells, respectively. Interestingly, the structurally related amphidinolides C2[4] (**2**) and F[5] (**3**) display significantly reduced activities against these cell lines (0.8 and 3 μg/mL, respectively, for **2**; 1.5 and 3.2 μg/mL, respectively for **3**), suggesting that the C(25)-C(34) side chain plays an important role in the bioactivity of amphidinolides C, C2, and F. As such, amphidinolide C is an important target for synthesis and exploration as a lead compound for drug development. Several efforts on the synthesis of **1**-**3** have appeared, including a report from our laboratory on the synthesis of the C(11)-C(29) fragment of amphidinolide F.[3b,6]

A retrosynthetic analysis of **1**-**3** is presented in Figure 1. We envisage that these targets can be assembled from the major fragments **4** and **5** via a late-stage cross-coupling and macrolactonization sequence (or esterification followed by macrocyclization via intramolecular cross-coupling). Both fragments **4** and **5** possess *trans*-tetrahydrofuran ring systems that appeared to be excellent targets for synthesis via chelate-controlled [3+2]-annulation[7] reactions of aldehydes and allylsilanes.[8] We have previously reported the

roush@scripps.edu.

synthesis of an advanced precursor to **4** via a [3+2]-annulation sequence.[6a] At the outset, we envisaged that the C(1)-C(9) fragment **5** could be assembled efficiently via the chelate-controlled [3+2]-annulation reaction of crotylsilane **6**[9] and an appropriate aldehyde coupling partner. In practice, a first-generation synthesis of **5a** (X = H) was developed that proceeds via the [3+2]-annulation reaction of **6** and **7**. Owing to the length of this first generation synthesis, we also developed a second generation sequence culminating in the synthesis of **5b** (X = H) via the intramolecular hetero-Michael addition of **8**. Both syntheses are presented herein.

Allylsilane **6** was prepared in 75-91% ee by the known enantioselective Rh(II) catalyzed insertion of the diazoester derived from **9** into the Si-H bond of phenyldimethylsilane (Scheme 1).[9] We initially targeted aldehydes **11** for use in chelate-controlled [3+2]-annulation reactions with **6**, since this would introduce the correct number of carbon atoms in the C(3) substituent of tetrahydrofuran **12**. The dithiane unit in **12a** and the benzyl ether in **12b** would also be sufficiently robust to survive the Hudrlik conditions[10] that we initially contemplated using for protiodesilylation of **12** (a milder protocol for protiodesilylation was subsequently developed).[11] However, all attempts to effect the chelate-controlled [3+2]-annulation reactions of **6** with either **11a** or **11b** and a variety of chelating Lewis acids ($SnCl_4$, $TiCl_4$, etc) failed to provide more than trace amounts of the 2,5-*trans*-tetrahydrofurans **12**; rather, the 2,5-*cis*-tetrahydrofuran isomer (not shown) was obtained preferentially, indicating that the dithiane and benzyl ether units of **11a,b** were incapable of forming a kinetically competent concentration of β-chelate with the aldehyde.[12]

The required 2,5-*trans*-THF stereochemistry was successfully accessed via the $SnCl_4$-promoted [3+2]-annulation reaction of crotylsilane **6** and ethyl glyoxalate (**7**) (Scheme 1). This reaction provided **13** in 82% yield with >20 : 1 diastereoselectivity. Further elaboration of **13** to the C(1)-C(9) fragment of amphidinolide C is summarized in Scheme 2.

Reduction of **13** with DIBAL followed by conversion of the primary alcohol to the mesylate and then to the corresponding iodide set the stage for a one-carbon homologation via alkylation with 2-lithio-l,3-dithiane.[13] This four-step sequence provided the 2,5-*trans*-THF **12a** in 74% overall yield. Protiodesilylation of **12a** using modified[8a] Hudrlik conditions (TBAF, KOtBu, DMSO, H_2O, 18-crown-6)[10] effected simultaneous deprotection of the primary TBS ether. Subsequent oxidation (SO_3-pyridine, DMSO)[14] of the primary alcohol gave aldehyde **14**. Treatment of this intermediate with Brown's γ-borylallylborane **15**[15] then gave *anti*-diol **16** in 47% yield with ca. 5:1 diastereoselectivity. Protection of the diol as a bis-TBS ether set the stage for dithiane deprotection (MeI, $KHCO_3$, MeCN).[16] Chlorite oxidation[17] of the C(1)-carboxaldehyde and esterification of the resulting carboxylic acid provided ester **17** (same as **5a**, X = H) in 34% yield for the four steps. Finally, ozonolysis of **17** provided the amphidinolide C C(1)-C(9) aldehyde **18** in 76% yield.

This synthesis of **18** proceeds in 13 steps from crotylsilane **6** in ca. 7% overall yield (17 steps from commercial precursors, including the synthesis of **6**). This synthesis of **18** was too lengthy for an intermediate of such modest complexity, with seven steps devoted to elaboration of the methoxycarbonyl group of tetrahydrofuran **13**. Thus, our inability to effect the chelate-controlled [3+2]-annulation reaction of **6** and **11a** or **11b** proved to be quite costly. We therefore decided to pursue a second generation approach, in which the *trans*-THF unit is assembled via the intramolecular hetero-Michael cyclization of **8** (see Scheme 3).

The second generation sequence began with the Horner-Wadsworth-Emmons olefination of glyceraldehyde isopentylidene ketal **19**[18] using the Still-Genari reagent. [19] This provided *Z*-enoate **20** with >96:4 Z:E selectivity. Acid catalyzed deprotection of the pentylidene ketal and spontaneous in situ lactonization of the γ-hydroxy ester, followed by diastereoselective hydrogenation of the butenolide double bond[20] and protection of the primary alcohol gave

lactone **21** with 20:1 diastereoselectivity. DIBAL reduction of **21** gave the corresponding lactol, which was converted to **8** by treatment with the stabilized ylide $Ph_3P{=}CHCO_2Me$.

Treatment of **8** with TBAF in THF effected the intramolecular Michael cyclization with simultaneous deprotection of the TBS ether, and provided tetrahydrofuran **22** with 9:1 diastereoselectivity in 84% yield (Scheme 4). An analogous cyclization was reported by Kobayashi and coworkers during their stereochemical assignment work on amphidinolide C.[3c] This transformation evidently proceeds under kinetic control, as treatment of the minor tetrahydrofuran diastereomer **23** with TBAF in THF at ambient temperature did not provide any **22**. The diastereoselectivity of the kinetically controlled cyclization of **8** can be rationalized by minimization of $A_{1,3}$-strain in transition state A.[21]

Tetrahydrofuran **22** was elaborated to the amphidinolide C C(1)-C(9) fragment **28** as summarized in Scheme 5. Oxidation of **22** with DMSO-pyridine under Parikh-Doering conditions[13] gave aldehyde **24**. Allylboration of **24** with the second genaration γ-borylallylborane **25** developed in our laboratory[22] provided diol **26** with 92 : 8 diastereoselectivity. Diol **26** was then protected as the bis-TBS ether **27** (same as **5b**, X = H). Ozonolysis of **27** then gave aldehyde **28**, which differs from aldehyde **18** (Scheme 2) only with respect to the ethyl versus a methyl ester. This second generation synthesis of **28** was completed in 11 steps from aldehyde **19** (13 from commercial materials) in 21% overall yield.

In summary, we have developed two syntheses of the C(1)-C(9) fragment of amphidinolide C. The first generation synthesis involving the chelation-controlled [3 + 2]-annulation reaction of **6** and glyoxylate **7** provided 2,5-*trans*-tetrahydrofuran **13** that was elaborated to the C(1)-C(9) fragment **18** by an 11-step sequence (Scheme 2). However, this effort was compromised by the inability to effect chelate-controlled [3+2]-annulations with aldehydes **11a** or **11b**, which would have led to a much shorter synthesis of **18** if successfully implemented. Consequently, a more efficient second-generation synthesis of the C(1)-C(9) fragment **28** was developed that proceeds via the kinetically controlled Michael cyclization of **8** (Scheme 5). The latter sequence is the one that we now use for bringing up material in onging efforts to complete total syntheses of amphidinolides C, C2, and F. Studies along these lines will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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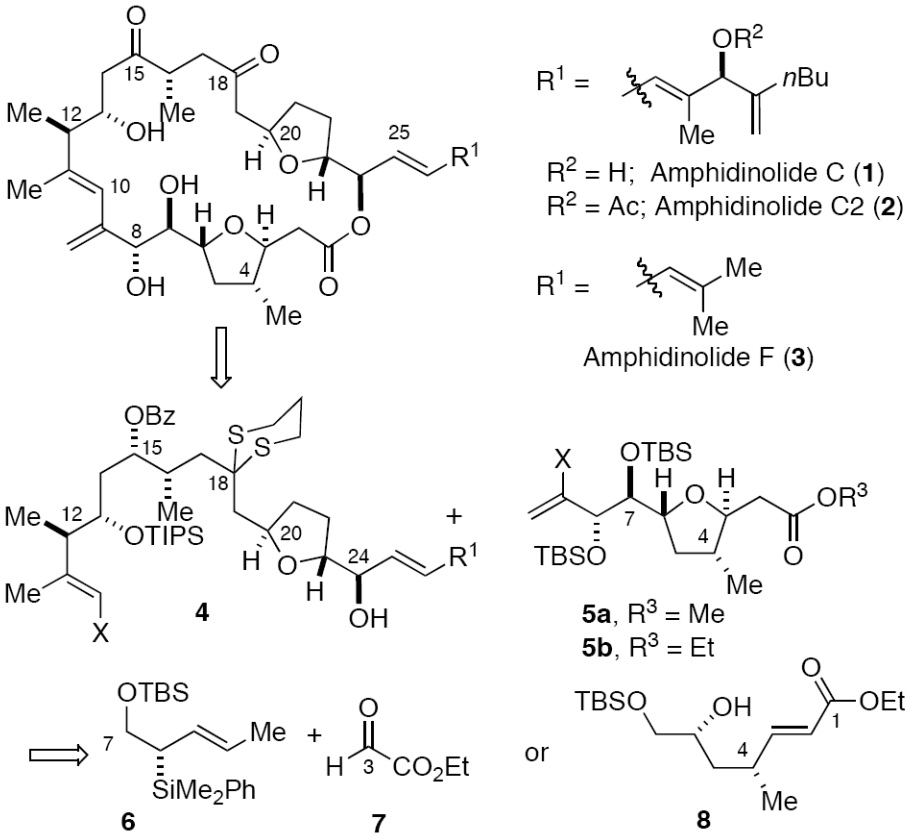
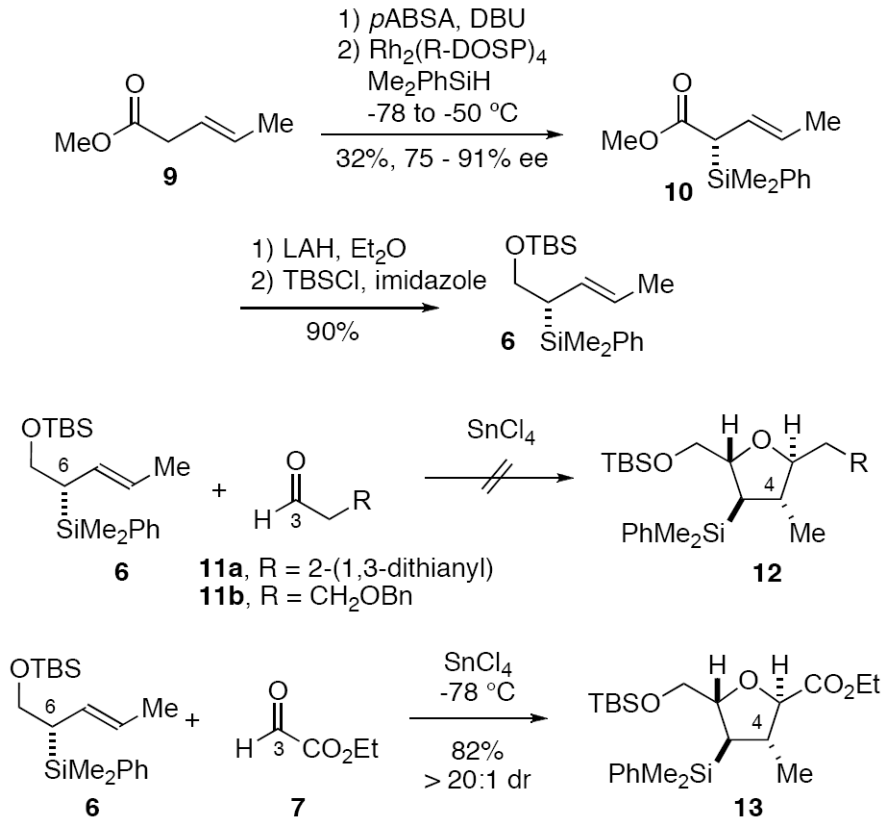
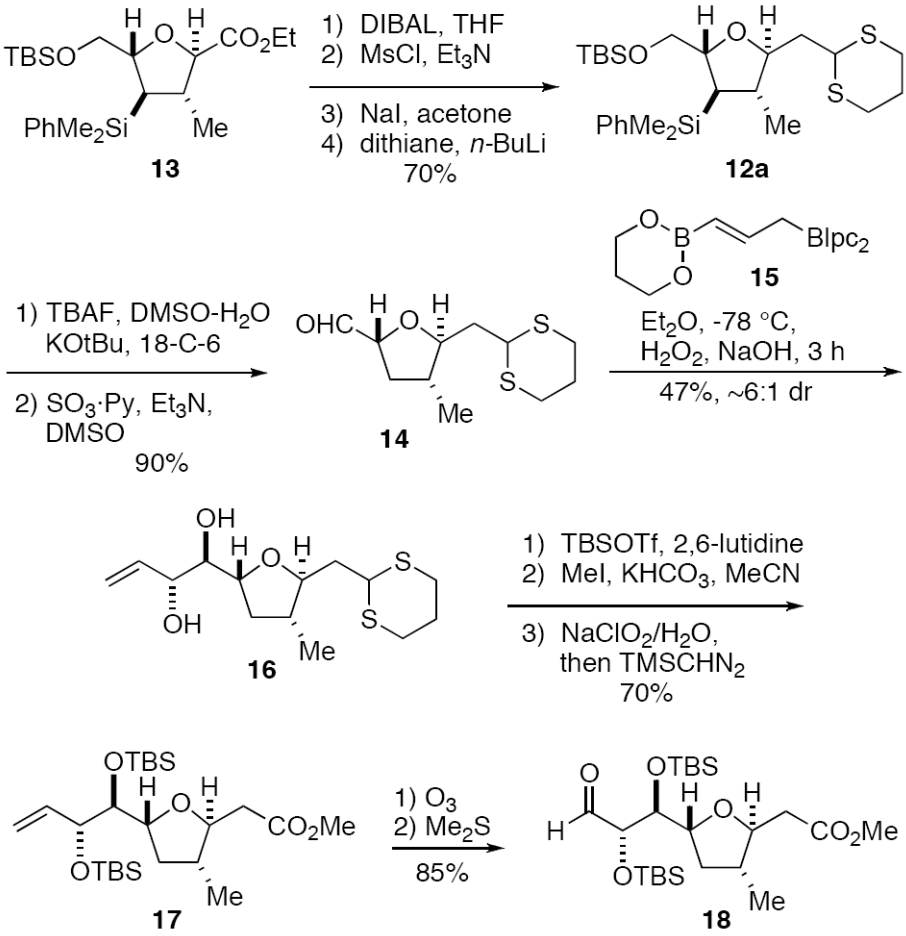


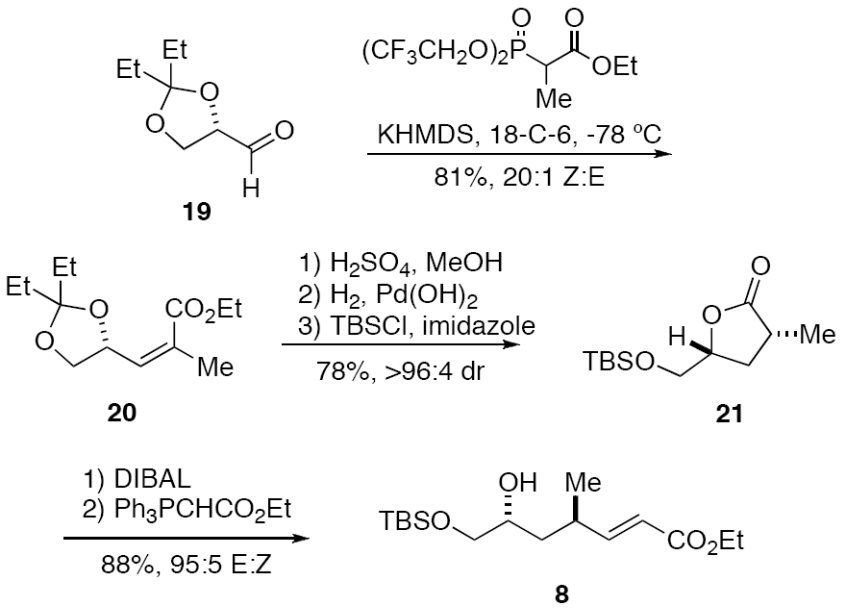
Figure 1.
Amphidinolide C, retrosynthetic analysis



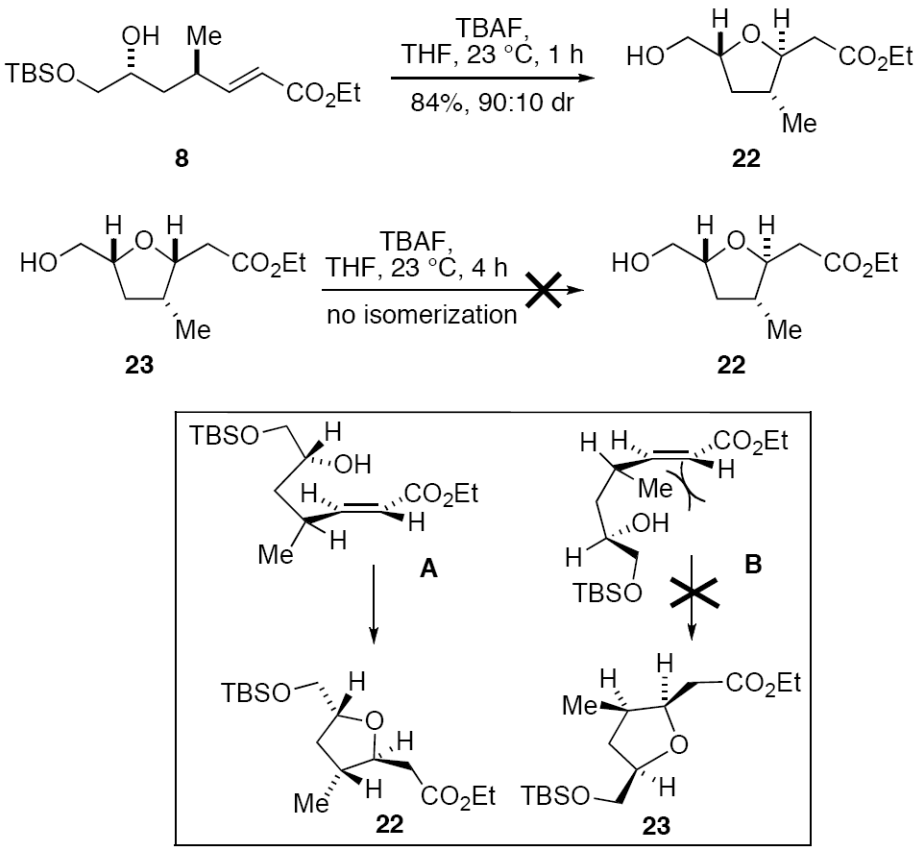
Scheme 1.
Synthesis of tetrahydrofuran **13** via [3+2]-annulation reaction of **6** and **7**



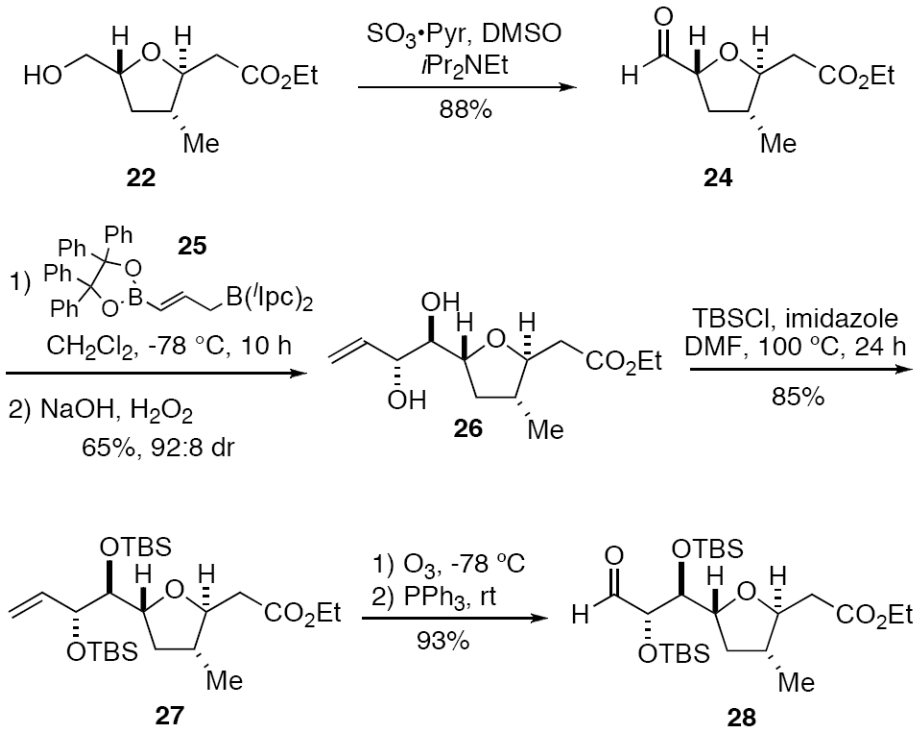
Scheme 2.
First generation synthesis of the C(1)-C(9) fragment **18** of amphidinolide C.



Scheme 3.
Synthesis of cyclization substrate **8**



Scheme 4.
TBAF-promoted cyclization of **8**



Scheme 5.

Completion of the second generation synthesis of the C(1)-C(9) fragment **26** of amphidinolide C.