Studies of the Enantiocontrolled Synthesis of the C(10)–C(25) Subunit of Amphidinolide C

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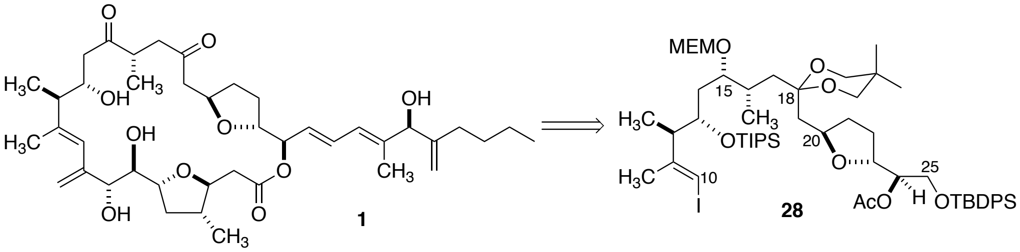
Supporting Information Placeholder



ABSTRACT: A stereocontrolled synthesis of the C_{10}–C_{25} component **28** of amphidinolide C (**1**) has been efficiently achieved. Reaction of the dithiane component **21** with nonracemic bis-epoxide **19** directly affords the functionalized 2,5-*trans*-disubstituted tetrahydrofuran **22**. Propargylation is highly diastereoselective for the formation of the desired C_{12}–C_{13} *anti*-stereochemistry, and the resulting terminal alkyne **25** is utilized for a regioselective *syn*-silylstannylation. A general strategy is illustrated for sequential replacement of stannyl and silyl substituents of the trisubstituted alkene to yield *E*-alkenyl iodide **28**.

Amphidinolide C (**1**) was first described by Kobayashi and coworkers in 1988 as a unique twenty-five membered macrolactone isolated from the symbiotic dinoflagellate *Amphidinium sp.* which is found in the host Okinawan flatworm, *Amphiscolops sp*.[1] Limited availability of this natural product delayed the assignment of stereochemical features until sufficient quantities were isolated from cultured dinoflagellates in 2001.[2] Similar structural characteristics are present in amphidinolide C2 (**2**), as well as amphidinolide C3, which displays the corresponding C-29 ketone.[2] Amphidinolide C demonstrates potent cytotoxic activity with IC_{50} values against murine lymphoma L1210 and KB carcinoma 0.0058 and 0.0046 µg/mL, respectively. The amphidinolides represent a diverse collection of macrolides.[3] Related metabolites include amphidinolide F (**3**) which shares the structural features of the macrocycle subunit of **1** with a simplified carbon side chain (Figure 1).[4] Amphidinolide U (**4**) is a twenty-membered macrolide possessing the same side chain as found in **1**.[5] The bioactivity of **3** is reportedly 1.5 µg/mL against lymphoma L1210 cells, and the modest cytotoxicity of **4** (IC_{50} = 20 µg/mL in the KB assay) indicates the importance of a combination of features in the macrocycle as well as in the carbon chain that account for the high potency. This information suggests a dual mode of binding involving key recognition elements of the macrocycle accompanied by an adjacent site for binding of the functionalized side chain.[6] Related characteristics have previously been described for a number of actin-based marine cytotoxins.[7] Actin is the most abundant structural protein of eukaryotic cells and is vitally important in a range of essential processes including tissue morphogenesis, cell growth and differentiation, cell death and responses to external stimuli. Recent studies have determined that amphidinolide H is covalently bound at Tyr200 on actin subdomain 4 and stabilizes F-actin.[8] Thus, the amphidinolides may uncover important targets to probe the regulation of actin dynamics as well as novel leads for drug development.[9]

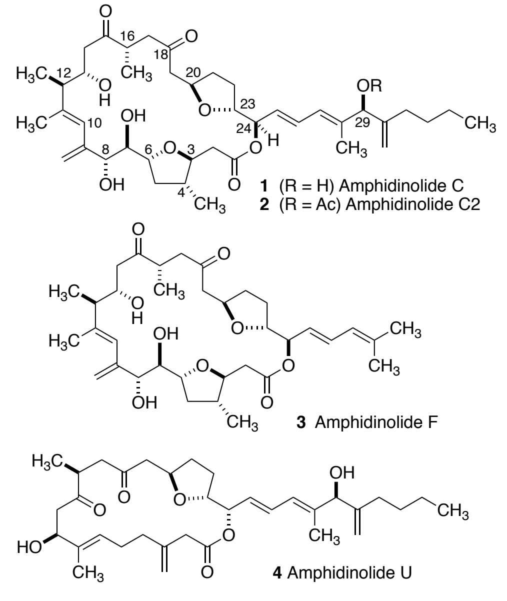
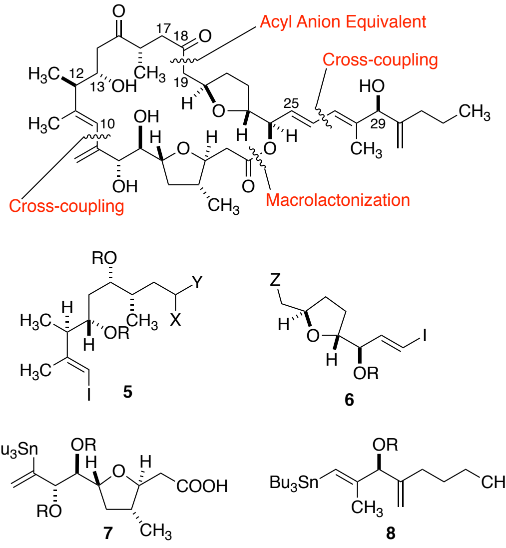


Figure 1. Amphidinolide C and related metabolites.

A number of laboratories have communicated advances of methodology directed towards the syntheses of fragments of amphidinolide C and its related macrolides.[10] In 2012, Mahapatra and Carter completed the first total syntheses of amphidinolide F and shortly thereafter, amphidinolide C.[11] Fürstner and coworkers described a ring-closing alkyne metathesis strategy for the successful synthesis of **3** in 2013.[12] Subsequently, Fürstner developed this novel concept to achieve the elegant synthesis of amphidinolide C (**1**) itself.[13] Herein, we describe an efficient, enantiocontrolled synthesis of the fully functionalized C(10)–C(25) fragment of (**1**). Our approach highlights the use of a chiral, nonracemic bis-epoxide for one-step construction of the 2,5-*trans*-disubstituted tetrahydrofuran of the C_{10}–C_{25} component with efficient stereocontrol.

Significant features of our plan are diagrammed in the retrosynthetic analysis of **1** to give four strategic disconnections. The protocols designated in Figure 2 suggest an assembly of components **5**, **6**, **7** and **8** to provide an effective route to the natural product **1** which would also be amenable to prepare interesting congeners for biological studies.



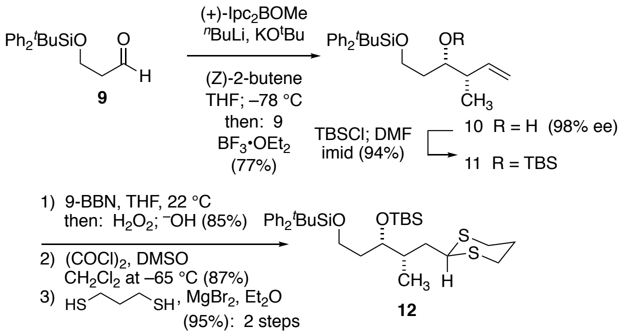
[R = protecting groups]

Figure 2. Retrosynthetic considerations.

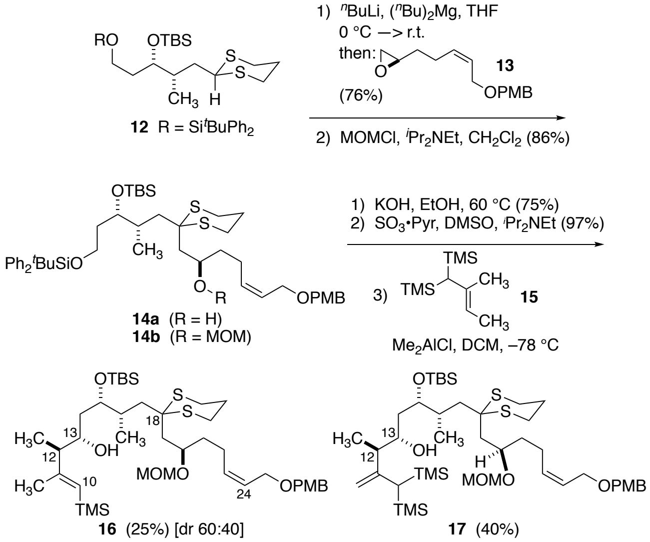
Our synthesis studies of the C_{10}–C_{25} fragment of amphidinolide C first focused on formation of the C_{18}–C_{19} bond via alkylation of a suitable acyl carbanion equivalent. Dithiane **12** was readily produced (Scheme 1) via the asymmetric Brown crotylation which gave the homoallylic alcohol **10** in 98% ee (≥ 99% de).[14] Protection and hydroboration of **11** directly afforded a primary alcohol for subsequent oxidation and thioacetal formation to yield the desired **12**.

The initial strategy of Scheme 2 failed to achieve our objectives, but provided important information for the successful pathway. We first examined the deprotonation of dithiane **12** and adapted a procedure described by Ide and Nakata,[15] which premixed di-*n*-butylmagnesium and *n*-butyllithium. These conditions proved very effective for complete deprotonation and significantly reduced the observed decomposition of the resulting carbanion as compared to the use of other strong bases. Introduction of the chiral epoxide **13**[16] at ambient temperature led to the desired alcohol **14a** (R = H; 76% yield), and subsequent protection resulted in the MOM-ether **14b**. We sought to incorporate our methodology for a Lewis acid-catalyzed $S_E{}'$ reaction with *E*-1,1-bis(trimethylsilyl)-2-methyl-2-butene (**15**)[17] to directly produce the *E*-alkenylsilane **16**.

Scheme 1



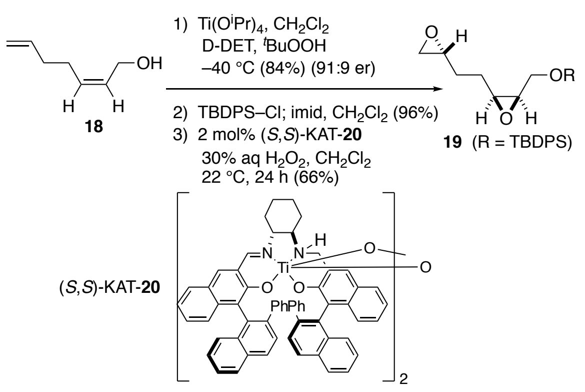
Scheme 2



Deprotection of **14b** and oxidation gave the expected aldehyde which was utilized in the Sakurai allylation at –78 °C. Unfortunately, reactions led to an inseparable mixture of *anti* **16** and its *syn* C_{12}–C_{13} diastereomer (25%; dr 60:40) in addition to the Alder ene product **17** (40%).[18] Optimizations to improve upon the poor chemoselectivity and stereoselectivity of these preliminary results were met with failure. To address these problems, we incorporated several changes that proved to be highly advantageous as documented in the successful strategy of Scheme 4.

The success of Scheme 4 was inspired by studies of biomimetic cascade reactions from polyepoxide precursors that have led to complex THFs and related heterocyclic systems.[19] Our previous studies of (+)-breynolide had demonstrated the use of a chiral bis-epoxide for sequential alkylation and direct cyclization.[20] However, the preparation of nonracemic **19** (Scheme 3) raised a number of issues due to its high reactivity with Lewis acids and nucleophilic bases. The synthesis of **19** is described via the Sharpless asymmetric epoxidation (SAE) of *Z*-allylic alcohol **18** followed by protection of the intermediate epoxyalcohol and subsequent Katsuki catalytic oxidation of the terminal olefin. Our preliminary studies have reported this strategy as an effective route for the enantioselective preparation of a variety of substituted THFs.[21] Asymmetric epoxidation of the monosubstituted alkene is accomplished using 2 mol% of the Katsuki titanium salen catalyst,[22,23] (*S*,*S*, KAT-**20**), in CH_2Cl_2 with dropwise addition of 30% aqueous H_2O_2 (1.5 equiv). Over 24 h, the reaction produces the nonracemic **19** as the principal component of a highly enantioenriched mixture of isomers (65% yield). Starting alkene is also

Scheme 3. Preparation of Nonracemic Epoxide 19

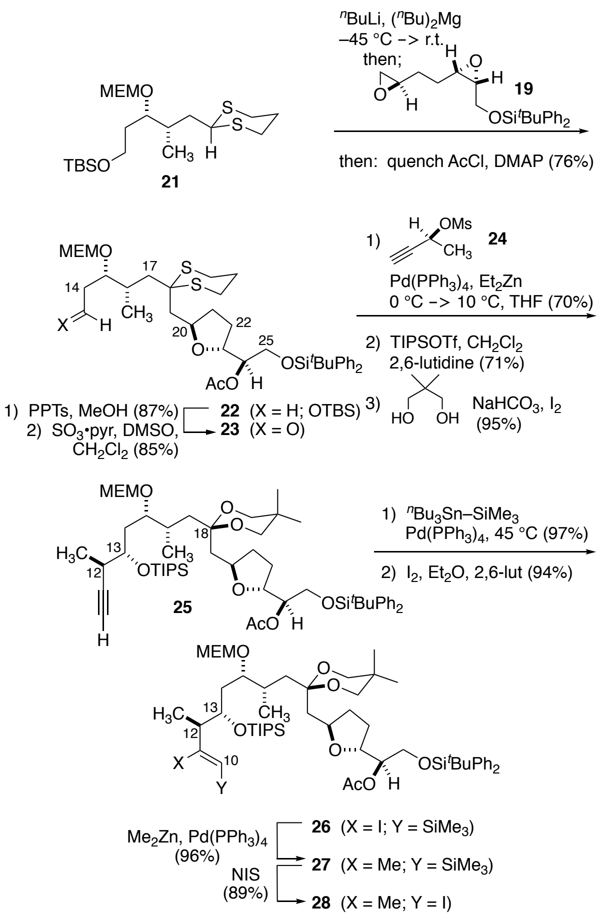


recovered by flash chromatography (20–25% yield) and is recycled with additional catalyst **20** and hydrogen peroxide to provide 80% overall conversion to **19** after two cycles.

Evaluation of ^{13}C NMR data of the product **19** indicates a 90:10 ratio of diastereoisomers,[24] and the use of this material in preparative scale reactions led to the separation of unwanted diastereomers in the next step. Enrichment studies under conditions of the Jacobsen hydrolytic kinetic resolution (HKR)[25] examined the use of MCPBA for the second epoxidation, and led to formation of **19** in 91:9 dr (see supporting information). The order of the epoxidation steps is essential as the Lewis acidity of titanium complexes in the SAE causes hydrolytic formation of THF products via facile destruction of desired product **19**. Chiral epoxide **19** was utilized in Scheme 4 following MEM protection at C-15 to afford dithiane **21**. Deprotonation of **21**, as previously described, and introduction of the bis-epoxide at 0 °C was followed by warming to ambient temperature and the addition of acetyl chloride and dimethylaminopyridine (DMAP). Upon flash silica gel chromatography, the condensation product **22** (76%) was readily purified with removal of small amounts of diastereomers.

Deprotection and oxidation of **22** afforded the pure C$_{13}$ aldehyde **23**. Further studies advanced the aldehyde **23** with excellent stereocontrol via the Marshall propargylation procedure.[26] The metallation of chiral mesylate **24** gave a nonracemic allenylzinc species for high facial selectivity in the production of the C$_{12}$–C$_{13}$ *anti*-stereochemistry (dr 10:1). The desired homopropargylic (C$_{13}$) alcohol was obtained as a single isomer in 70% yield following flash chromatography, and was used in subsequent attempts for a Negishi carboalumination[27] of the terminal alkyne. This procedure and related efforts[28] failed with notable decomposition of the acetal functionality. Protection of the C$_{13}$ alcohol as its tri-isopropylsilyl (TIPS) ether did not offer improvement. However, success was achieved by an efficient transketalization using 2,2-dimethyl-1,3-propanediol and iodine[29] to give alkyne **25** (95%) which underwent a regioselective palladium-catalyzed *syn*-silylstannation with tri-*n*-butylstannyltrimethylsilane.[30] This reaction is particularly advantageous because it features versatile conditions for the sequential replacement of the stannane and silane substituents with complete stereocontrol. Treatment of the intermediate vinyl stannane with iodine at 0 °C in ether with 2,6-lutidine affords the corresponding alkenyl iodide **26** in 94% yield, and a Negishi cross coupling[31] with dimethylzinc at 65 °C in the presence of Ph(PPh$_3$)$_4$ catalyst yields the *E*-alkenylsilane **27** (96%). Finally, the electrophilic replacement of trimethylsilyl with *N*-iodosuccinimide (NIS) has produced the desired C$_{10}$–C$_{25}$ segment **28** (89% yield).

Scheme 4



In summary, an efficient, enantiocontrolled route for synthesis of the C$_{10}$–C$_{25}$ segment of amphidinolide C has been developed. Our strategy features the use of the nonracemic bis-epoxide **19** to yield the fully functionalized 2,5-*trans*-THF of **22** in a single operation. The reaction of aldehyde **23** with a chiral allenylzinc species results in stereospecific propargylation to install the desired C$_{12}$–C$_{13}$ *anti*-relationship, and *syn*-silylstannylation of the alkyne **25** led to a convenient and versatile synthesis of the *E*-alkenyl iodide **28**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxx

Experimental procedures, spectroscopic data, and selected ^{1}H and ^{13}C NMR spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Ene product **17** is slowly converted into **16** by BF_3•OEt_2 as a single diastereomer. The stereochemistry of **16** at C(12)/C(13) is tentatively assigned by ^{1}H NMR comparisons with data for **27** of Scheme 4. We have included experimental descriptions and ^{1}H NMR data in the SI for this failed route.

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