

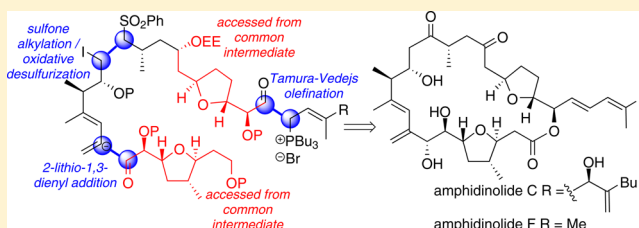
Exploiting Hidden Symmetry in Natural Products: Total Syntheses of Amphidinolides C and F

Subham Mahapatra and Rich G. Carter*

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, United States

Supporting Information

ABSTRACT: The total synthesis of amphidinolide C and a second-generation synthesis of amphidinolide F have been accomplished through the use of a common intermediate to access both the C₁–C₈ and the C₁₈–C₂₅ sections. The development of a Ag-catalyzed cyclization of a propargyl benzoate diol is described to access both *trans*-tetrahydrofuran rings. The evolution of a Felkin-controlled, 2-lithio-1,3-dienyl addition strategy to incorporate C₉–C₁₁ diene as well as C₈ stereocenter is detailed. Key controlling aspects in the sulfone alkylation/oxidative desulfurization to join the major subunits, including the exploration of the optimum masking group for the C₁₈ carbonyl motif, are discussed. A Trost asymmetric alkynylation and a stereoselective cuprate addition to an alkynoate have been developed for the rapid construction of the C₂₆–C₃₄ subunit. A Tamura/Vedejs olefination to introduce the C₂₆ side arm of amphidinolides C and F is employed. The late-stage incorporation of the C₁₅, C₁₈ diketone motif proved critical to the successful competition of the total syntheses.



INTRODUCTION

Natural products continue to yield medicinally relevant leads for the treatment of human disease¹ as well as an inspiration for the development of new synthetic strategy and chemical methodology for their construction.² Macrolides such as epothilones,³ apoptolidins⁴ and bryostantins⁵ historically have provided a rich source of inspiration in both of these areas. The amphidinolide family of macrolides embodies another such collection of natural products that provides synthetic inspiration through their challenging architecture with equally intriguing biological function—particularly cytotoxic activity against multiple cancer cell lines.⁶

While multiple total syntheses of many members of this family have been reported,⁷ certain important subfamilies remain unaddressed. Of these unaddressed subfamilies, our laboratory became particularly interested in amphidinolides C and F, as they possess challenging (and identical) macrocyclic core and intriguing biological profile (Figure 1). Both amphidinolides C and F have attracted considerable synthetic attention⁸ including from our own laboratory;⁹ however, no total synthesis of either compound had been reported prior to our efforts.^{10,11} Amphidinolide C was isolated from the genus *Amphidinium* (Y-5, Y-56, Y-59 and Y-71 stains) in extremely small amounts (0.0015% yield) by Kobayashi and co-workers.¹² The relative stereochemistry of **1** was determined by 1D and 2D NMR techniques and the absolute stereochemistry was established through degradation and Mosher ester analysis.¹² **1** exhibits impressive cytotoxic activity in multiple cancer cell lines (murine lymphoma L1210 cells: IC₅₀ = 5.8 ng/mL and human epidermoid carcinoma KB cells: IC₅₀ = 4.6 ng/mL).¹² Subsequently, additional variants (amphidinolides C₂ and C₃)

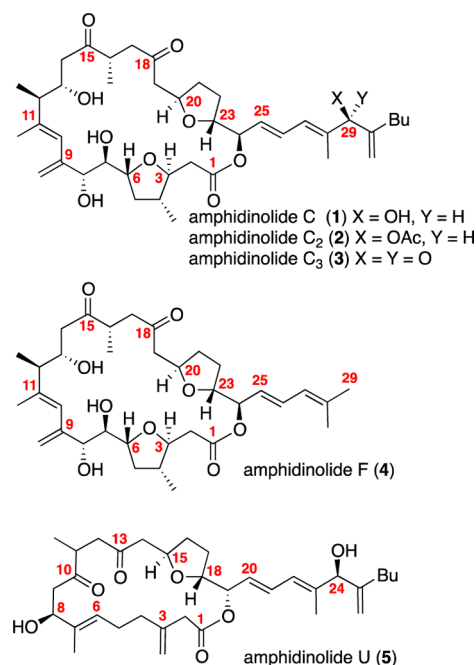


Figure 1. Amphidinolides C, F and U.

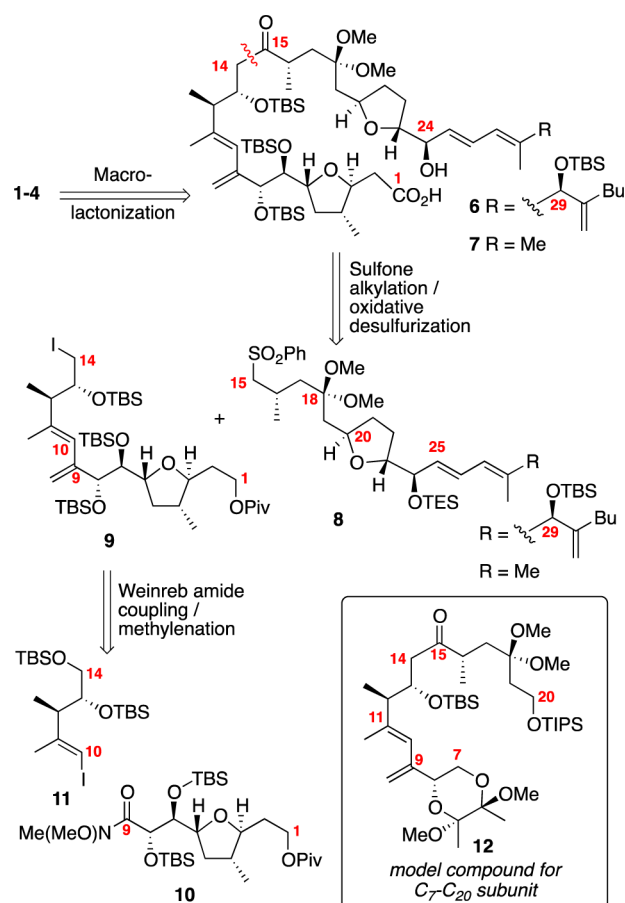
have been identified which bear esterification or oxidation at C₂₉.¹³ Kobayashi has also reported the isolation of amphidinolide U (**5**). This compound contains the same side

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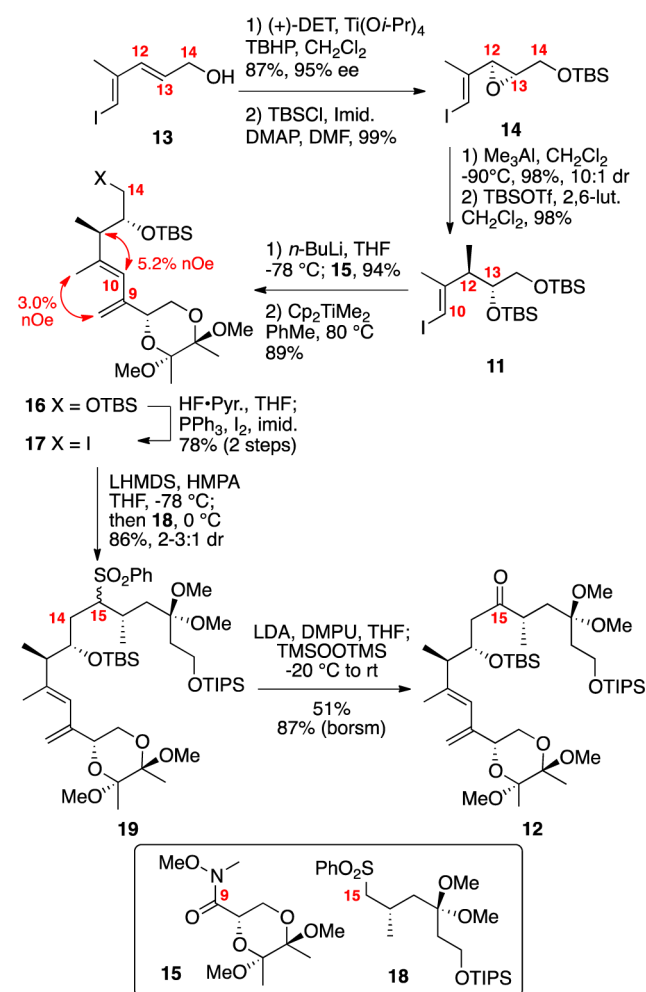
■ RESULTS AND DISCUSSION

Scheme 1. Retrosyntheses for Amphidinolides C–C₃ and F



Our successful studies^{9a} on model compound **12** embarked from the readily available dienyl iodide **13**²¹ (Scheme 2).

Scheme 2. Synthesis of C₇–C₂₀ Segment: A Model Study

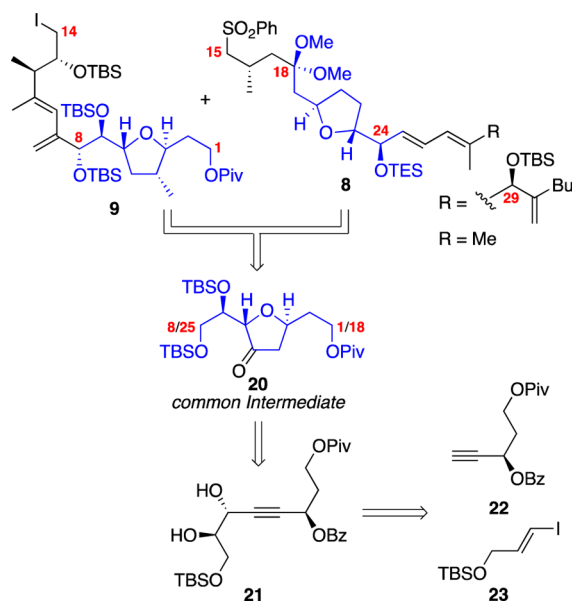


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removal of the C₁₄ TBS ether and conversion to iodide provided the requisite coupling partner **17**. Next, our attention turned to the key sulfone alkylation/oxidative desulfurization sequence. The sulfone **18** (prepared in 9 steps from 3-hydroxy-(2*R*)-methylpropionic acid methyl ester^{9a}) was lithiated with LHMDS in the presence of HMPA and added to iodide **17** to cleanly provide the C₁₄–C₁₅ coupled material **19** in good yield as a mixture of diastereomers at C₁₅. Given the sterically congested nature of both the nucleophile and electrophile, the high efficiency of this coupling was rewarding. Next, the oxidative desulfurization on sulfone **19** was examined. After some experimentation, we found that deprotonation with LDA in the presence of DMPU followed by the addition of TMSOOTMS produced the desired ketone **12** in 51% isolated yield (87% borsm).

With an understanding that our strategy for the diene portion and coupling the two major subunits was likely to prove successful, we started our efforts toward the synthesis of the two THF segments (Scheme 3). Central to this strategy

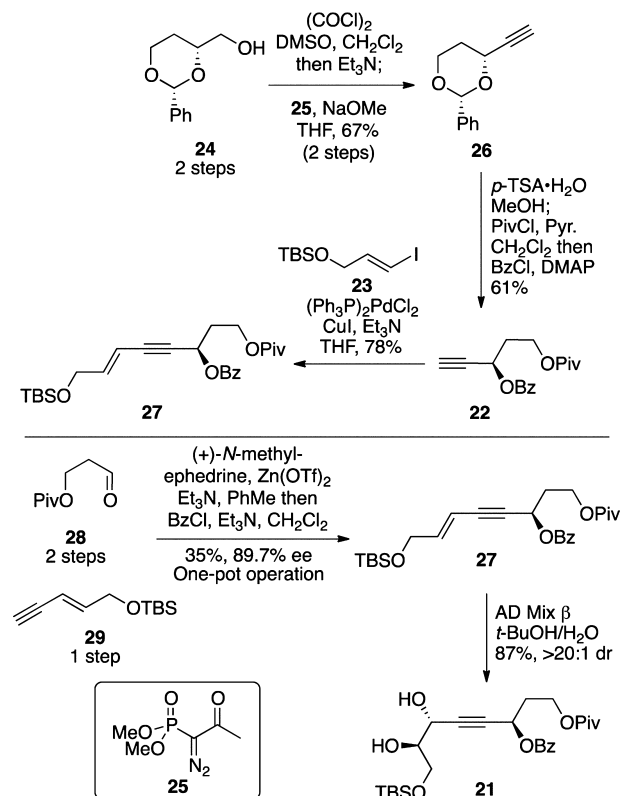
Scheme 3. Common Intermediate Approach to Major Subunits



was the observation that a hidden symmetry element was present within the macrocyclic core. The functionality and stereochemistry of C₁–C₈ mapped nicely on the C₁₈–C₂₅ subunit. The lone exception to this correlation was the presence of the C₄ methyl moiety. We identified that both the major fragments **9** and **8** could arise from a common subunit **20**. This subunit in turn should be accessible from the propargyl benzoate/diol **21** through a metal-catalyzed cyclization. Pioneering work by Krause²⁴ and Gagosz²⁵ had demonstrated that Au- or Ag-catalyzed processes were feasible; however, neither Krause nor Gagosz has tested the potential of this chemistry on diol systems such as **21** or in the presence of considerable additional functionality.

Synthesis of the cyclization precursor **21** is shown in Scheme 4. Starting from the known alcohol **24** (available in two steps from D-malic acid),²⁶ Swern oxidation followed by alkyne formation using the Ohira-Bestmann reagent **25** provided **26**. The alkyne **26** could also be accessed from the aldehyde via the two-step Corey-Fuchs protocol (Ph₃P, CBr₄, CH₂Cl₂; *n*-BuLi,

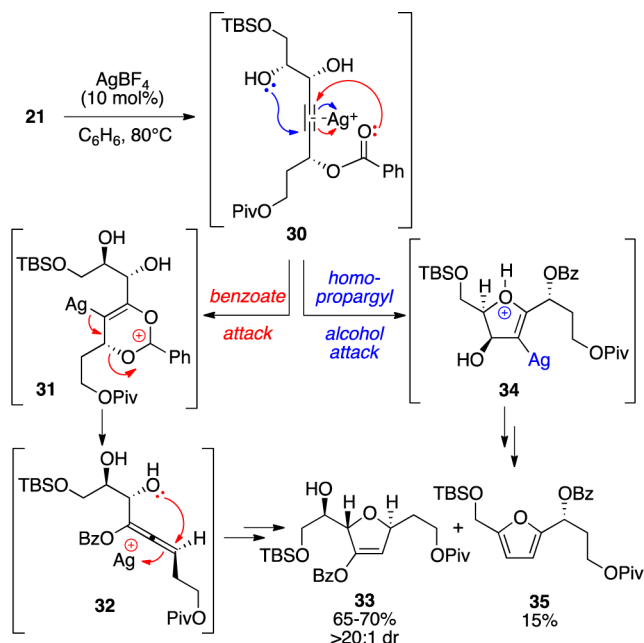
Scheme 4. Synthesis of Cyclization Precursor



THF, 69% over 2 steps). Diol deprotection and subsequent esterifications provided the propargyl benzoate **22**. Sonogashira coupling²⁷ with known vinyl iodide **23**²⁸ generated the enyne **27**. While this seven-step route provided access to the enyne **27** in multigram quantities, a more expedient route was feasible through the known aldehyde **28**²⁹ and enyne **29**³⁰ using Carreira's asymmetric alkynylation³¹ with *in situ* benzoate ester formation to provide **27** in four fewer steps (LLS). Sharpless dihydroxylation with AD Mix β^{32,33} provided the cyclization precursor **21** in high yield and excellent dr.

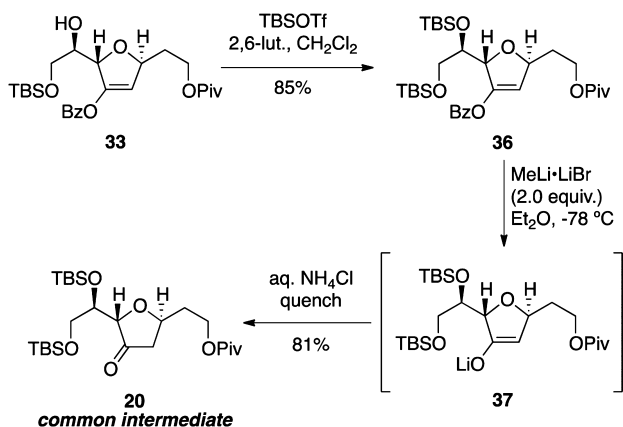
We were pleased to find that the desired metal-catalyzed cyclization could be cleanly effected by treatment of **21** with AgBF₄ (10 mol %) in degassed benzene at 80 °C to produce the *trans*-DHF **33** in 65–70% yield on 5 g scale (Scheme 5). Interestingly, Au-catalyzed versions of this cyclization proved unsuccessful in our hands. Key to this transformation was the absence of light; performing this transformation in a lighted room led to greatly diminished yield (~25%). Selection of the pivaloyl protecting group was also key as use of electron-rich moieties (e.g., PMB, DMB) led to reduced yield (0–30%). In addition to the desired DHF **33**, a small amount (15%) of the furan byproduct **35** was also produced. We hypothesize that nucleophilic attack by the benzoate oxygen (marked in red) on activated alkyne **30** might produce the allene species **32** via stabilized carbocationic intermediate **31**. Another silver-mediated activation of allene **32** could promote the nucleophilic attack by proximal alcohol moiety to deliver the DHF **33** after protodemetalation. Alternately, byproduct **35** might arise from a competitive attack by the distal hydroxyl nucleophile on activated alkyne **30** (marked in blue) to generate the vinyl silver intermediate **34**. Protodemetalation followed by Lewis (or Bronsted) acid-activated aromatization would produce the furan **35**.

Scheme 5. Silver-catalyzed Cyclization to Dihydrofuran

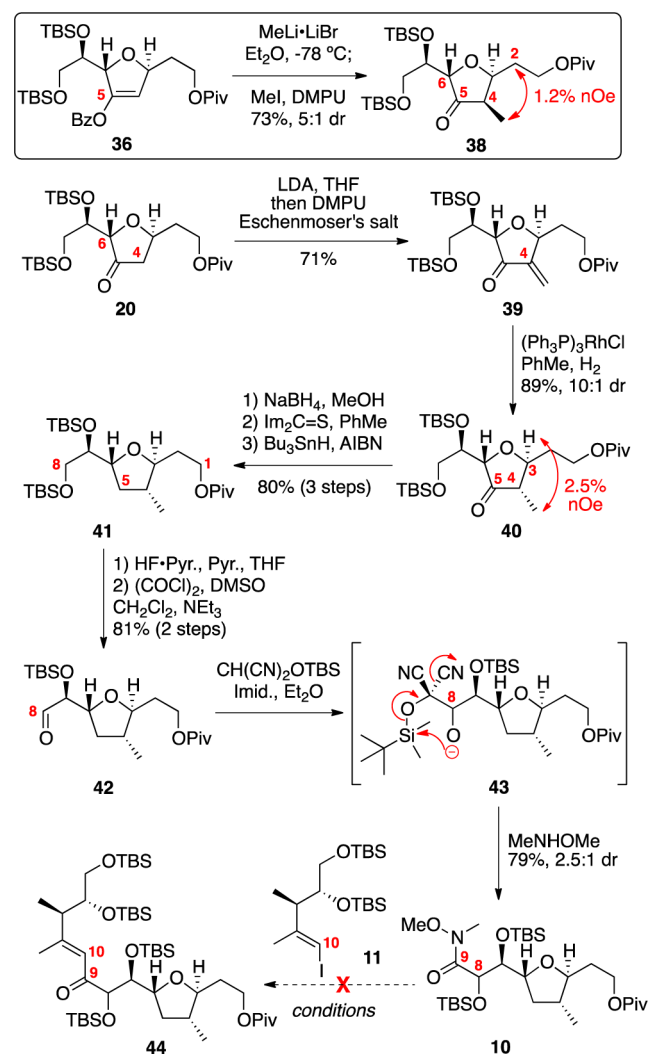


Synthesis of the common intermediate **20** is shown in Scheme 6. While alcohol **33** proved to be unstable to prolonged storage, protection as its TBS ether **36** quickly addressed that shortcoming. Removal of the benzoate ester in presence of the pivalate (Piv) moiety was problematic. Fortunately, we found that treatment with modulated methyl lithium ($\text{MeLi}\cdot\text{LiBr}$)³⁴ provided conditions that selectively cleaved the benzoate moiety to reveal the *in situ* enolate **37** which was protonated with aqueous ammonium chloride to provide the common intermediate **20**. A small amount of the pivalate deprotected product (~10%) was observed under these conditions; however, use of MeLi instead of $\text{MeLi}\cdot\text{LiBr}$ led to significantly larger amount of depivaloated product.

Scheme 6. Synthesis of the Common Intermediate



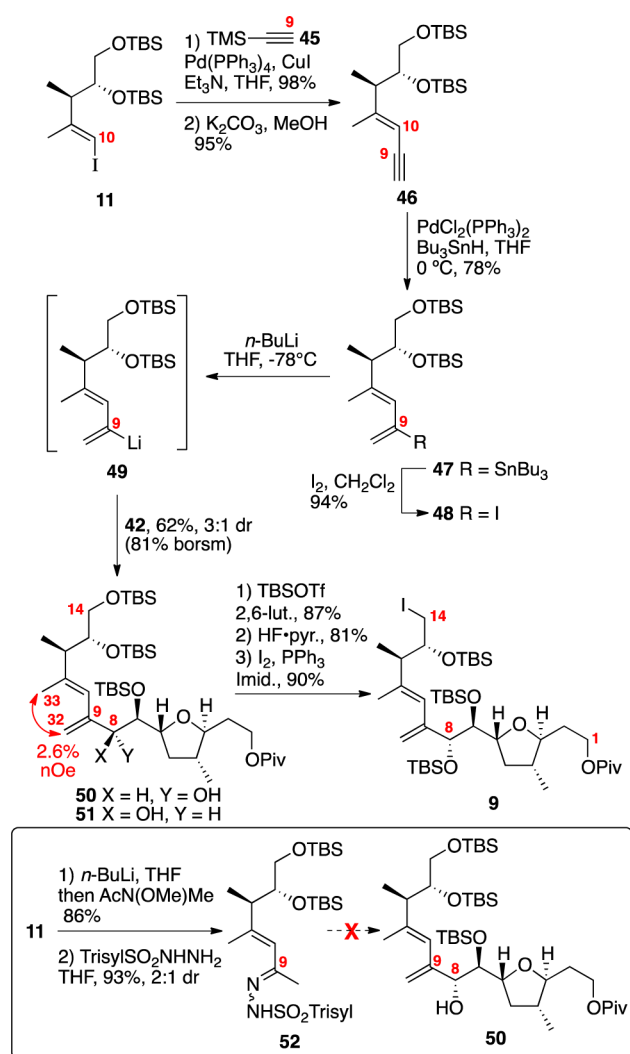
With the common intermediate **20** in hand, we first set out to develop a general approach to the C_1 – C_{14} portion of both amphidinolides **C** and **F** (Scheme 7). While we had hoped that simple alkylation of the enolate **37** (e.g., generated *in situ* from $\text{MeLi}\cdot\text{LiBr}$ treatment of benzoate **36**) would provide the desired stereochemical outcome, we experimentally observed the undesired C_4 stereochemistry in 5:1 dr. Interestingly, the C_6

Scheme 7. Initial Approach for C_1 – C_{14} Subunit

stereocenter overrode the more proximate C_3 position to control the stereochemistry of this transformation. This stereochemical bias was successfully harnessed by first methylenation of the ketone **20** using Eschenmoser's salt followed by hydrogenation with Wilkinson's catalyst to give the desired stereochemical combination in 10:1 dr. In both cases **38** and **40**, the C_4 stereochemistry was determined by nOe analysis. Next, deoxygenation of ketone **40** was first explored using a Wolff–Kishner strategy. Myers had recently reported an elegant improvement³⁵ to the traditional harsh conditions for this transformation that appeared well-suited to our substrate. While we were able to form the TBS-hydrazone intermediate, we were unable to effect the necessary reduction—leading only to decomposition or no reaction under a variety of conditions. We next turned to a Barton–McCombie strategy.³⁶ Reduction of the ketone to alcohol followed by conversion to the thioate and Bu_3SnH -mediated reduction cleanly provided the deoxygenated product **41** in excellent overall yield.³⁷ It was important that the Bu_3SnH reduction be conducted in deoxygenated solvent. Next, removal of the C_8 TBS ether was cleanly effected using $\text{HF}\cdot\text{pyr.}$ conditions followed by Swern oxidation to yield the aldehyde **42**. In order to access the presumed coupling partner (e.g., **10**), it was required to incorporate the C_9 Weinreb amide and to establish the C_8 stereocenter. Nemoto

has reported an elegant potential solution for this challenge, which utilized a silyoxy malononitrile nucleophile.³⁸ We were pleased to see that these conditions nicely proceeded via the presumed intermediate **43**³⁹ to provide the Weinreb amide **10** in good yield and modest diastereoselectivity. While stereochemical outcome of this experiment was expected to be the Felkin (*syn*) product, we did not rigorously determine the C₈ stereochemistry. Unfortunately, despite considerable efforts using either the major or minor C₈ diastereomers, we were unable to facilitate the subsequent coupling experiment between the organolithium species derived from iodide **11** and the Weinreb amide **10** using a variety of halogen/metal exchange conditions (e.g., *n*-BuLi, *t*-BuLi) and solvents (THF, Et₂O, THF/hexanes). On the basis of these unexpected results, a revised approach was needed to circumvent the iterative formation of the C₈–C₉ and the C₉–C₁₀ bonds.

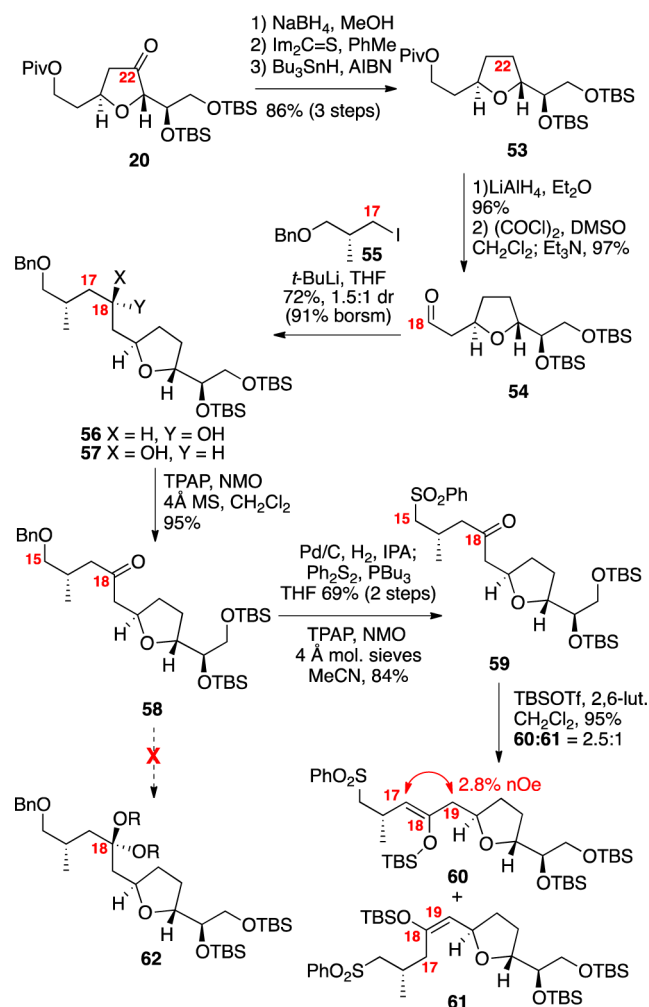
The successful synthesis of the C₁–C₁₄ subunit is shown in Scheme 8. In order to circumvent the problematic addition chemistry with Weinreb amide **10**, we chose to utilize a nucleophilic 1,3-diene motif (e.g., organolithium **49**) for diastereoselective addition to aldehyde **42**. We were unaware of any prior example of exploiting similar strategy with 2-lithio-1,3-dienes. While a related vinyl iodide have been employed in cross coupling strategy to form the diene motif present in

Scheme 8. Synthesis of the C₁–C₁₄ Subunit

amphidinolide **B**,⁴⁰ the organolithium strategy brought with its potential for metallotropic rearrangement⁴¹ of **49**. We initially explored accessing this lithio species via a Shapiro process from the corresponding hydrazone **52**; however, this approach led to rapid decomposition. We hypothesized that proportionately milder halogen-metal exchange process at lower temperature might circumvent this decomposition process. Thus, we targeted 2-iodo-1,3-diene **48** as a suitable precursor for accessing the lithiated species. In preparation for this strategy, Sonogashira coupling²⁷ between iodide **11** and TMS-acetylene (**45**) cleanly furnished the enyne **46** in excellent chemical yield. Use of a Pd(II) salts [e.g., (Ph₃P)₂PdCl₂] gave reduced chemical yields as compared to (Ph₃P)₄Pd. Next, Pd(0)-catalyzed hydrostannylation⁴² followed by iodination produced the dienyl iodide **48**. To our delight, halogen–metal exchange followed by addition of aldehyde **42** cleanly provided the targeted allylic alcohol **50** in 62% yield and 3:1 dr (**50**:**51**). This strategy allowed us to produce the 1,3-diene and secure the C₈ stereochemistry in a single operation. The C₈ stereochemistry was confirmed by advanced Mosher ester analysis.⁴³ After TBS protection at C₈, selective desilylation at C₁₄ and conversion to the corresponding iodide provided the C₁–C₁₄ subunit **9**.

With a viable, unified route to the C₁–C₁₄ domain, our attention shifted to construction of the remaining sulfone subunit (Scheme 9). Starting from the common ketone

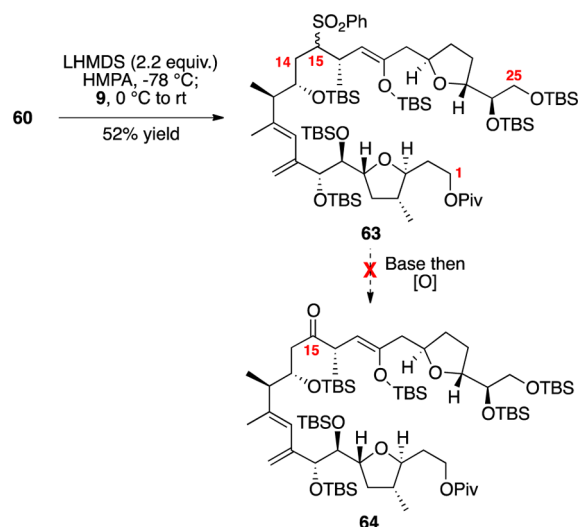
Scheme 9. Synthesis of the Silyl Enol-ethers



intermediate **20**, borohydride reduction provided corresponding alcohol as a 1.7:1 mixture at C₂₂. Thiolate formation under basic conditions led to silyl migration, but use of thermolysis in presence of thiocarbonyldiimidazole cleanly yielded the thiolate. Barton-McCombie deoxygenation proceeded smoothly to provide THF **53**. After, pivalate deprotection and Swern oxidation to yield aldehyde **54**, coupling with the organolithium species derived from iodide **55**⁴⁴ produced the alcohols **56/57** as a inseparable mixture of diastereomers. Attempted coupling the C₁₅ thiophenyl version⁴⁵ of **55** proved problematic in our hands. Oxidation generated the C₁₈ ketone **58**. As we had done previously,^{9a} we planned to mask the C₁₈ ketone as ketal **62**. Despite our considerable efforts, we were unable to affect this process. Consequently, it was necessary to develop an alternate method for masking the C₁₈ carbonyl moiety. One option was to construct a silyl enol-ether that should be readily cleavable under mild fluoride conditions; however, its utility was potentially complicated due to the possibility for formation of four different isomers. Fortunately, after conversion to the sulfone **59**, treatment with TBSOTf under mildly basic conditions cleanly produced just two of the four possible isomers in excellent yield.

We next set out to test the viability of our coupling strategy on the enol-ethers **60** and **61** (Scheme 10). After modification

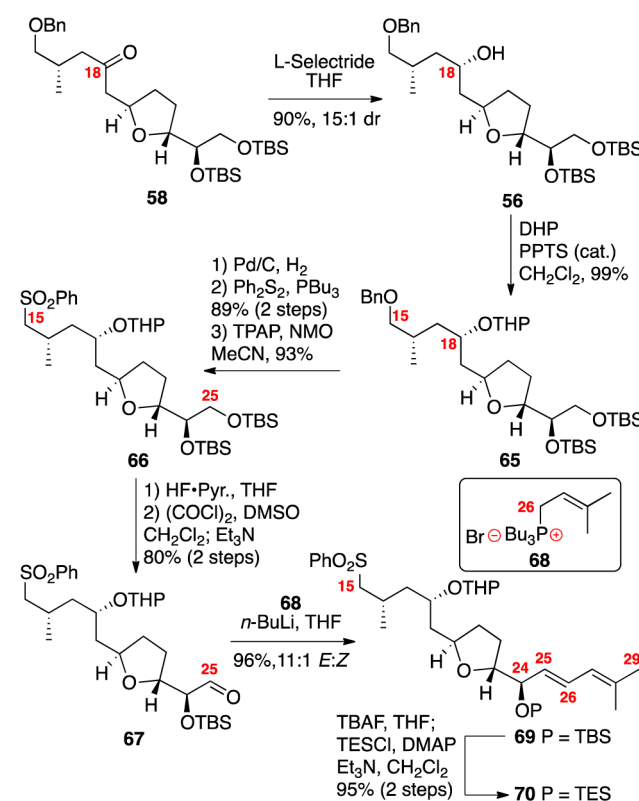
Scheme 10. Exploration of Silyl Enol-ether Series in Sulfone Alkylation/Oxidative Desulfurization Sequence



of the stoichiometry of base as compared to previously developed conditions, we were able to once again facilitate the key C–C bond-forming event. While the yields were modest in the coupling process [52% yield for **60** and 45% yield for **61** (not shown)⁴⁶], we were more focused on the critical oxidative desulfurization. We were disappointed to observe only decomposition under a range of conditions for this critical step using **63** as well as its silyl enol-ether isomer (not shown). One possible explanation for the divergence in reactivity between our model system **19** and the silyl enol-ether series was the absence of a chelatable group at C₁₈ to help direct lithiation at C₁₅ and stabilize any resultant anion.

Based on this speculative C₁₈-chelation hypothesis, we embarked on the synthesis of a fully functionalized C₁₅–C₂₉ system containing an appropriately selected protecting group at C₁₈ (Scheme 11). We strategically targeted amphidinolide F

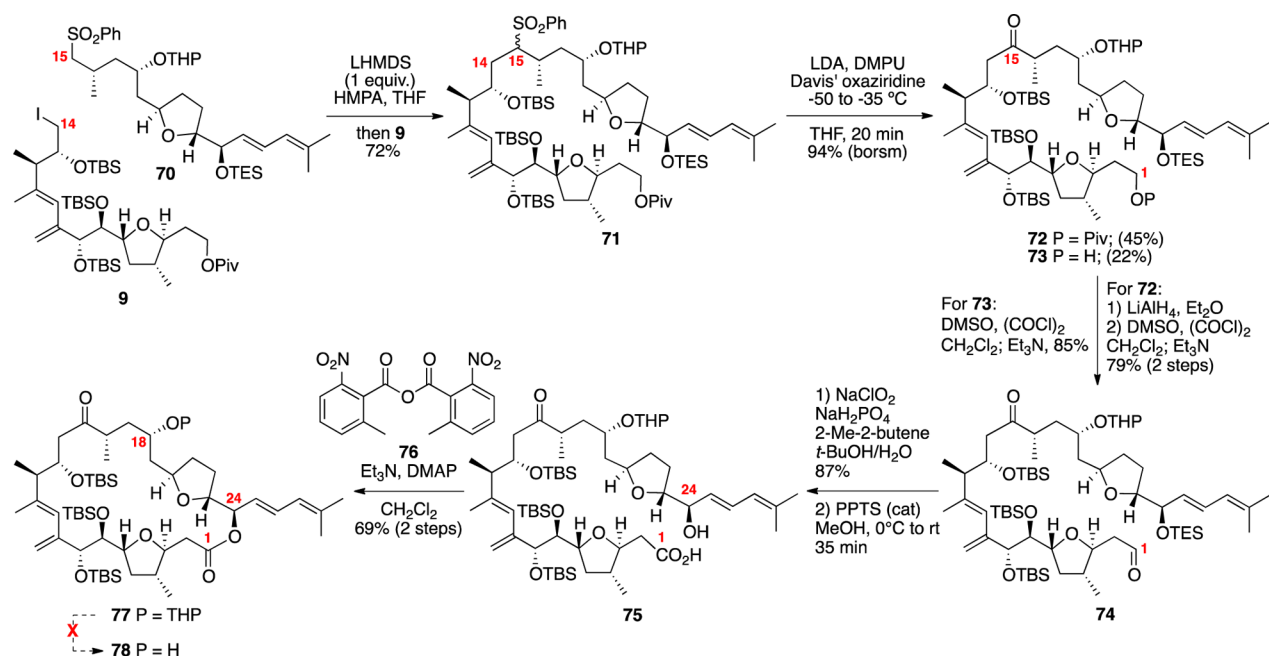
Scheme 11. Synthesis of the Tetrahydropyranyl Series



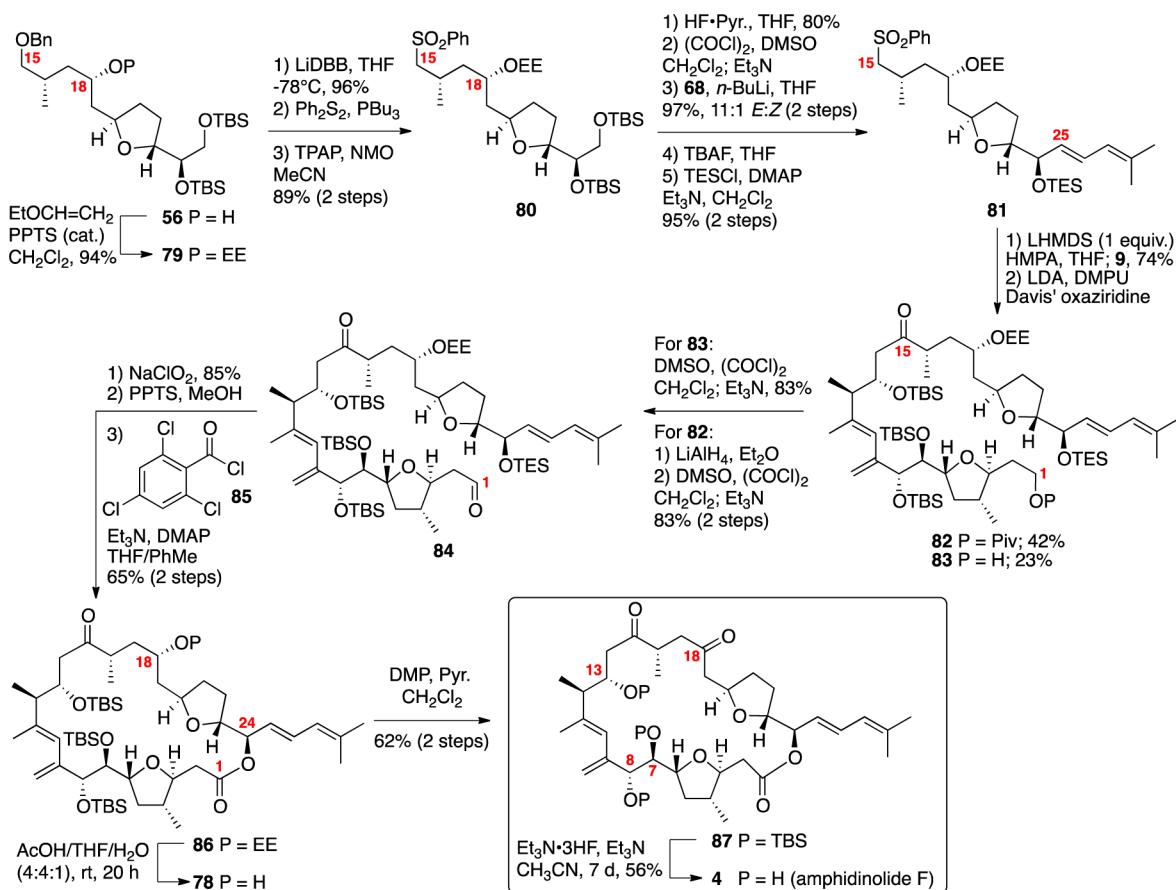
(4) first due to the C₂₅ simplified side arm with the expectation that lessons learned could be applied to amphidinolide C (**1**). Given the presumed acid sensitivity of the macrolactone, our choices were likely limited to protecting groups readily removable under mild conditions. We initially selected a THP protecting group at C₁₈ as it is well-known to be labile under mildly acidic conditions.⁴⁷ Starting from ketone **58**, L-Selectride reduction cleanly provided the 18S isomer **56** as determined by advanced Mosher ester analysis.⁴³ Protection at C₁₈ using DHP generated the mixed acetal **65** in excellent yield. Subsequent removal of the benzyl ether under hydrogenative conditions followed by sulfide incorporation and oxidation using TPAP, NMO in acetonitrile yielded the C₁₅ sulfone **66**. Selective removal of the C₂₅ TBS ether followed by Swern oxidation yielded the α -oxy aldehyde **67**. Olefination using the Tamura/Vedejs-type tributylphosphonium salt **68**⁴⁸ cleanly produced the desired diene **69** with high E/Z selectivity and chemical yield (96%, 11:1 E/Z). C₂₄ protecting group exchange produced the necessary coupling partner **70** in excellent yield.

With both the major subunits in hand, we set out to explore the critical sulfone alkylation/oxidative desulfurization sequence (Scheme 12). To our delight, treatment of sulfone **70** with LHMDS in presence of HMPA followed by addition of the iodide **9** yielded the C₁₄–C₁₅ coupled material **71** in a gratifying 72% yield. Only one equivalent of base with respect to sulfone **70** was necessary to effect the transformation. For the oxidative desulfurization, a modification of our original conditions provided the desired ketone in excellent overall yield. Davis' oxaziridine appeared to be key to this transformation as use of alternate oxidants (e.g., MoOPH, TMSOOTMS etc.) gave inferior results. Presence of the C₁₈ chelating protecting group is likely key to the success of both the alkylation and the oxidative desulfurization. Both the C₁

Scheme 12. Initial Construction of Amphidinolide F Macrocycle



Scheme 13. Total Synthesis of Amphidinolide F



Piv-protected and deprotected products (72 and 73 respectively) were obtained from this transformation (likely due to adventitious water facilitating its saponification); however, both compounds were productive contributors to the synthetic sequence. For 73, Swern oxidation directly produced the

aldehyde 74. For 72, LiAlH₄ reduction removed the pivalate with concomitant reduction of the C₁₅ carbonyl and subsequent oxidation under Swern conditions generated the same aldehyde 74. Pinnick oxidation provided the carboxylic acid. Next, we required the selective deprotection of the C₂₄ TES ether in

presence of multiple 2° TBS ethers and a OTHP moiety. Fortunately, mild acidic conditions (PPTS, MeOH) selectively removed the C₂₄ TES ether to provide seco acid **75**. We speculated that the sterically congested nature of the C₁₈ OTHP group inhibited its deprotection under these conditions. Little did we know that this positive short-term accomplishment was foreboding of future events. Next, macrolactonization of seco-acid **75** under Shina conditions⁴⁹ provided the 25-membered macrolactone **77** in good yield (69% over 2 steps). Yamaguchi macrolactonization conditions⁵⁰ were also effective in this transformation—albeit in a slightly lower chemical yield (65%). Despite the THP moiety's well-known lability under Brønsted and Lewis acidic conditions, we were unable to successfully facilitate its removal under a range of conditions 5:1:1 AcOH/THF/H₂O, MgBr₂,⁵¹ Me₂AlCl,⁵² BF₃•OEt₂/1,2-ethanedithiol⁵³—ultimately leading to decomposition in each case. We speculated that the acid sensitivity of the macrocycle **77** was due to preferential ionization at C₂₄, which would generate a highly stabilized dienyl cation.

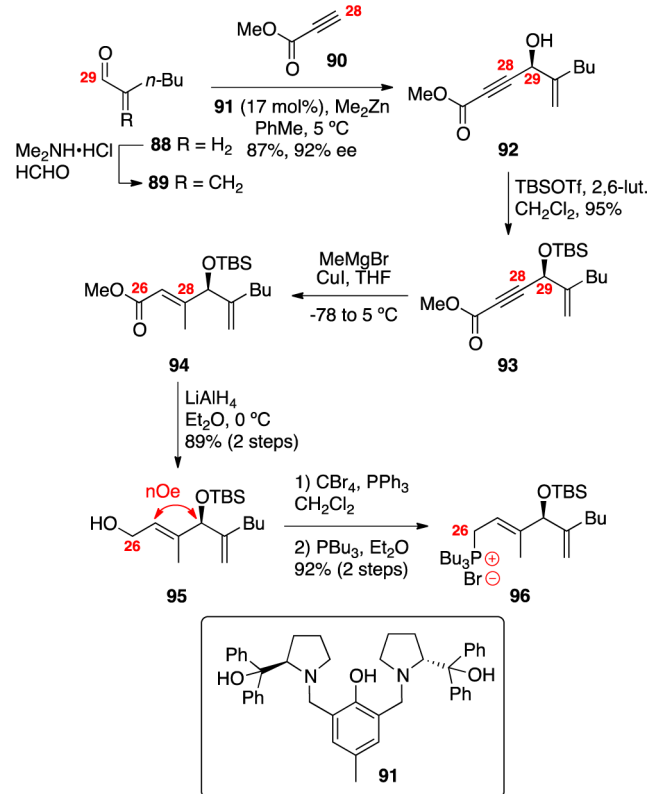
Despite this significant setback to our campaign toward amphidinolide F, two negative results provided a possible pathway to circumvent this reactivity. Unlike other conditions screened, treatment of **77** with either 4:2:1 AcOH/THF/H₂O or PPTS/MeOH⁵⁴ did not decompose the macrocycle (nor was any appreciable deprotection of the C₁₈ OTHP observed). We hypothesized if we could identify a more acid labile protecting group at C₁₈ that could be cleaved with these mildly acidic conditions, we could access the needed alcohol at that position. We cautiously turned to the underutilized ethoxyethyl ether (OEE) protecting group as a possible candidate. The OEE moiety is known to be significantly more labile than an OTHP group (ca. 250 times in one study)⁴⁷ while maintaining the necessary chelating ability for the sulfone alkylation/oxidative desulfurization sequence.

The successful execution of this C₁₈ OEE strategy for the total synthesis of amphidinolide F is shown in Scheme 13. Acetalization was best accomplished with PPTS and ethoxyvinyl ether in high yield. We quickly became concerned with the viability of this route, as the next required transformation (C₁₅ debenzoylation) proved problematic under our prior Pd/C, H₂ conditions (see Supporting Information). Use of the Freeman reagent⁵⁵ nicely circumvented the problem. Fortunately, the subsequent sequence principally followed our prior OTHP route. After formation of the required sulfone **81**, sulfone alkylation/oxidation proceeded in near identical yields to our OTHP route. For the macrocyclization, it was found the Yamaguchi conditions⁵⁰ to be optimum for accessing **86** in 65% yield over 2 steps. With the key macrocycle **86** in hand, we returned to the previously problematic C₁₈ deprotection. We were thrilled to find that our OEE hypothesis proved valid as aqueous acetic acid conditions smoothly provided the corresponding C₁₈ alcohol **78**. This alcohol **78** existed as a mixture of the hydroxyl ketone and C₁₅ hemiketal; however, the equilibrium could be driven to the C₁₅, C₁₈ diketone **87** by oxidation using Dess–Martin's periodinane (DMP). It is important to note that while macrolactonization, EE deprotection and DMP oxidation proceeded smoothly, NMR analysis of the corresponding macrolactones often generated broaden spectral patterns—indicating a conformational equilibrium likely existed on the NMR time scale. We explored multiple deprotection conditions for the three remaining TBS ethers (e.g., HF•pyr., TASF⁵⁶); however, prolonged exposure to Et₃N•3HF⁵⁷ ultimately proved to be effective—yielding

amphidinolide F (**4**) in 56% isolated yield. Spectral comparison of synthetic amphidinolide F was in good agreement with the spectral data (¹H, ¹³C, [α]_D) reported by Kobayashi and co-workers. It should be noted that both Kobayashi⁵⁸ and our own laboratory observed some concentration dependent shifts to the NMR spectra; however, comparison at 0.0036 M concentration (0.4 mg **4** in 0.18 mL CDCl₃) proved optimum. Thus, the total synthesis of **4** was achieved starting from 1,3-propanediol in 29 steps longest linear sequence (LLS) based on our second-generation route employing the Carreira asymmetric alkynylation sequence (Scheme 4).

We next set out to apply this overall strategy to the synthesis of the most bioactive member of this subfamily **1–4**, amphidinolide C (**1**). In fact, macrolide **1** is one of the most biologically potent members of the entire amphidinolide family of >35 macrolides. Our approach toward this compound employs the identical C₁–C₁₄ subunit **9**, but a more complicated sulfone coupling partner **99**. Starting from known aldehyde **89** [available in one-step from hexanal (**88**)⁵⁹], Trost asymmetric alkynylation⁶⁰ with commercially available alkyne **90** gave the desired propargyl alcohol **92** in high yield and enantioselectivity (Scheme 14). After silyl

Scheme 14. Synthesis of the Phosphonium Salt

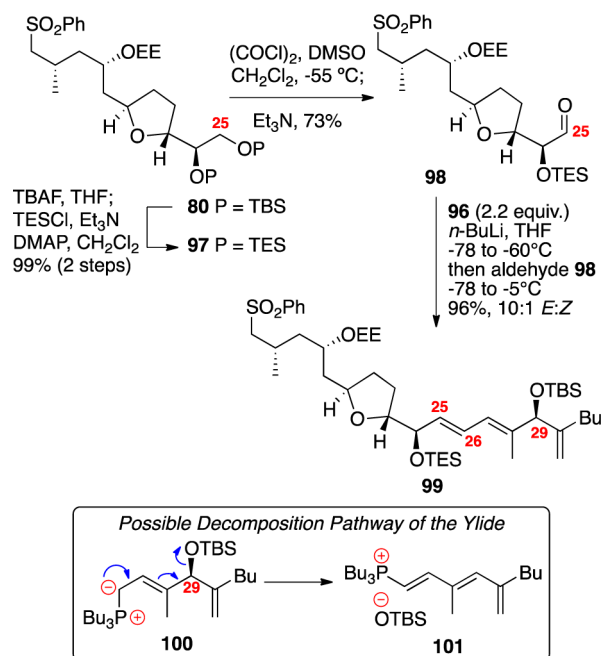


protection at C₂₉, cuprate addition to the alkynoate **93** generated the desired *E*-alkene **94** in complete stereoselectivity. LiAlH₄ reduction produced the allyl alcohol **95** in 89% yield over two steps. This compound was employed to determine the absolute configuration at C₂₉ by desilylation (TBAF) and advanced Mosher ester analysis.⁴³ Conversion of alcohol **95** to the corresponding tributylphosphonium salt **96** was accomplished by treatment with CBr₄, Ph₃P followed by displacement with PBu₃ in high overall yield. The overall route proved highly

efficient (6 steps, 68% overall yield) yielding the salt **96** in multigram quantity.

Synthesis of the C₁₅–C₃₄ sulfone **99** is shown in Scheme 15. Starting from previously made bis-TBS ether **80**, TBAF

Scheme 15. Synthesis of the Sulfone Subunit



mediated desilylation followed by bis-TES protection produced **97**. Next, tandem C₂₅ deprotection and oxidation using Swern conditions produced the α -oxy aldehyde **98**. We initially screened our previously optimized Tamura/Vedejs olefination conditions for attaching the necessary side arm; however, only decomposition was observed. This outcome was not entirely unexpected as base-induced elimination of ylide **100** would generate a conjugated triene **101**. Fortunately, reduction of the reaction temperature and an increase in the equivalence of the

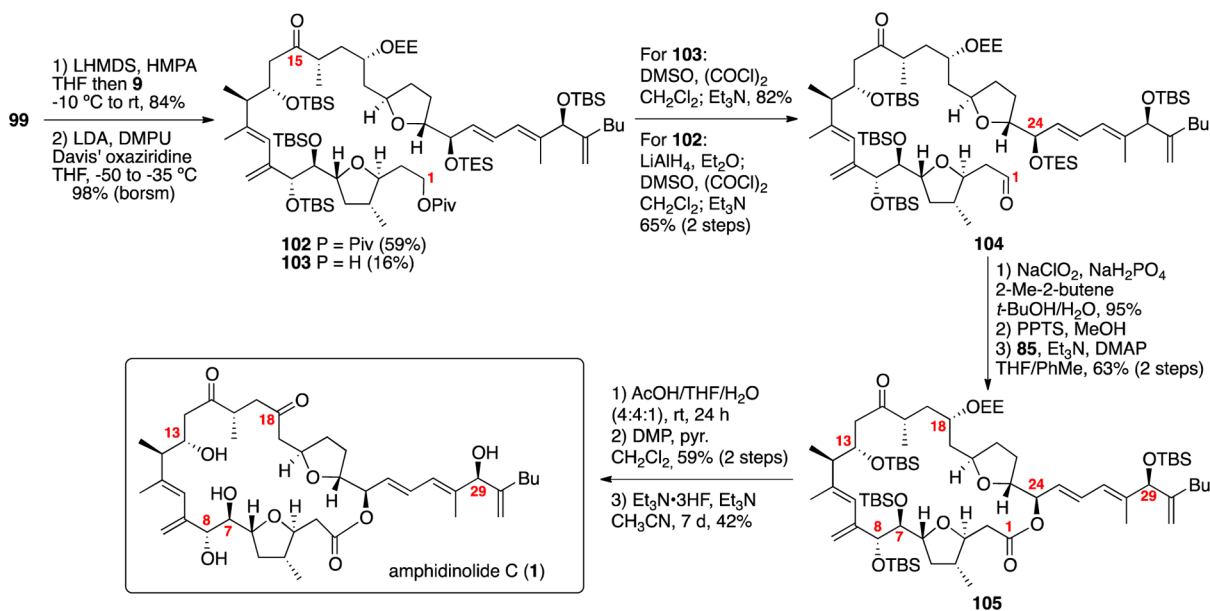
salt **96** (1.5 to 2.2 equiv) led to excellent conversion to the desired triene **99** (96% yield, 10:1 *E*/*Z*).

The completion of the total synthesis of amphidinolide C is shown in Scheme 16. Lithiation of sulfone **99** followed by addition of the iodide **9** generated the C₁₄–C₁₅ coupled material in excellent yield (84%). Oxidative desulfurization proceeded smoothly using LDA, DMPU and Davis' oxaziridine to produce 59% of **102** and 16% of **103**. As before, both compounds were useful for accessing the aldehyde **104**. Pinnick oxidation of aldehyde **104** followed by careful removal of the C₂₄ TES ether generated the seco acid. Yamaguchi macro-lactonization produced the 25-membered macrolactone **105** in 63% yield over two steps. Aqueous acetic acid conditions again proved effective for selective removal of the C₁₈ OEE moiety. Subsequent oxidation using DMP yielded tetra-TBS protected amphidinolide C. Gratifyingly, global deprotection using Et₃N•3HF produced the natural product **1**, which was matched nicely with the observed spectra (¹H, ¹³C NMR in C₆D₆).^{12b,c} Additionally, the optical rotation data was in agreement with the literature value [Synthetic: [α]_D²³ = -98.5° (*c* = 0.21, CHCl₃); Natural:¹² [α]_D²⁶ = -106° (*c* = 1.0, CHCl₃)]. This approach constitutes a 28-step synthesis (LLS) of amphidinolide C (**1**).

CONCLUSION

The total syntheses of amphidinolides C and F have been accomplished (28 and 29 LLS respectively). Central to these syntheses is the use of a common intermediate strategy to access approximately 65% of the macrocyclic core and the THF rings present in the two natural products. A stereoselective silver-catalyzed cyclization of a propargyl benzoate/diol was employed to construct the needed *trans*-stereochemistry of the THF rings. A Felkin-controlled, 2-lithio-1,3-dienyl addition to an α -silyloxy aldehyde incorporated the C₉–C₁₁ diene and established the C₈ stereocenter in single operation. An efficient 6-step sequence provided access to the C₂₆–C₃₄ aphidinolide C subunit and the Tamura-Vedejs olefination incorporated the C₂₅–C₂₉ side arm of amphidinolide F and the C₂₅–C₃₄ side arm of amphidinolide C. A sterically congested sulfone

Scheme 16. Total Synthesis of Amphidinolide C



alkylation/oxidative desulfurization sequence was utilized to couple the major subunits and incorporate the C₁₅ ketone. The presence of chelating moiety at C₁₈ was critical to the success of the oxidative desulfurization step. A carefully orchestrated sequence for stepwise revealing of the C₂₄ alcohol followed by macrolactonization, C₁₈ deprotection and oxidation provided access to the protected amphidinolide natural products. The final global deprotection was uniquely feasible utilizing Et₃N•3HF as desilylating agent. With a viable route to accessing the amphidinolide C/F subfamily, this work opens the door to exploring the pronounced influence of the C₂₅ side arm on biological activity. These studies will be reported in due course.

■ ASSOCIATED CONTENT

■ Supporting Information

Complete experimental procedures are provided, including ¹H and ¹³C spectra, of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

rich.carter@oregonstate.edu

Notes

The authors declare no competing financial interest.

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