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

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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 C_1-C_8 and the C_{18}-C_{25} 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 C_9-C_{11} diene as well as C_8 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 C_{18} 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 C_{26}-C_{34} subunit. A Tamura/ Vedejs olefination to introduce the C_{26} sidearm of amphidnolides C and F is employed. The late-stage incorporation of the C_{15}, C_{18} 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 disease[1] as well as an inspiration for the development of new synthetic strategy and chemical methodology for their construction.[2] Macrolides such as epothilones,[3] apoptolidins[4] and bryostantins[5] 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 attention[8] 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 coworkers.[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

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ASSOCIATED CONTENT

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

cells: IC_{50} = 5.8 ng/mL and human epidermoid carcinoma KB cells: IC_{50} = 4.6 ng/mL).[12] Subsequently, additional variants (amphidinolides C_2 and C_3) have been identified which bear esterification or oxidation at C_{29}.[13] Kobayashi has also reported the isolation of amphidinolide U (**5**). This compound contains the same side arm as amphidinolide C (**1**), but a simplified version of the macrocyclic core and has shown significantly reduced cytotoxicity data.[14] Amphidinolide F (**4**) has also been isolated in limited qualities (0.00001% wet weigh yield) bearing an identical macrcocyclic core, but with a simplified sidearm.[15] Interestingly, amphidinolide F shows greatly reduced cytotoxic activity as compared to **1**.[15] While the relative and absolute configurations of amphidinolide C had been established by Kobayashi, the definitive confirmation of the absolute stereochemistry of amphidinolide F and its relationship to amphidinolide C was not established until our laboratory completed its total synthesis in 2012.[10] In this article, we provide a full account of our synthetic efforts towards amphidinolide F as well as the first reported total synthesis of amphidinolide C.

Results and Discussion

Our retrosynthetic strategy for accessing amphidinolides C and F is shown in Scheme 1. We envisioned formation of the 25-membered macrocycle through Yamaguchi macrolactonization. Next, we planned to join the two major subunits and incorporate the C_{15} carbonyl through a sulfone alkylation / oxidative desulfurization sequence.[16] The nucleophilicity of sulfone carbanions is a powerful tool for the construction of sterically congested linkages such as the C_{14}-C_{15} bond, in which branching at neighboring C_{13} and C_{16} would normally inhibit such strategies.[17] Oxidative desulfurization is a chemical transformation that has been known for decades;[18] however, it has received comparatively limited attention for the synthetic community.[19] This umpolung approach also would allow us to regulate when the C_{15} carbonyl is incorporated while avoiding potential complications with dithiane chemistry.[20] The iodide **9** could be accessed from the vinyl iodide **11** and Weinreb amide **10** by an organolithium coupling followed by methylenation. Prior to embarking on the total syntheses of compounds **1–4**, we felt it would be prudent to study both our C_9-C_{11} diene strategy and sulfone alkylation / oxidative desul-furization sequence on a C_7-C_{20} model compound **12**.

Our successful studies[9a] on the model compound **12** embarked from the readily available dienyl iodide **13**[21] (Scheme 2). Sharpless epoxidation[22] followed by silyl protection produced **14**. Me_3Al-mediated opening of vinyl iodide / allyl epoxide **14** provided preferential S_N2 opening at C_{12}.[23] Our originally published conditions proved somewhat scale de- pendent,[9a] but we found that modified conditions (portion-wise addition of reduced equivalents of $AlMe_3$ and lowered reaction temperature to −90°C) gave reliable results on gram scale (>1.5 g scale, 98%, 10:1 dr). Subsequent silylation of C_{13} alcohol provided **11**. Halogen / metal exchange and coupling with the Weinreb amide **15**[9a] followed by methenylation using Petasis conditions yielded the diene **16** with no observable *E/Z* isomerization. 1D nOe analysis confirmed that the desired olefin geometry was present after methylenation. Selective removal of the C_{14} 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-hydrox-(*2R*)-methylpropionic acid methyl ester[9a]) was lithiated with LHMDS in the presence of HMPA and added to iodide **17** to cleanly provide the C_{14}-C_{15} coupled material **19** in good yield as a mixture of diastereomers at C_{15}. 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 towards the synthesis of the two THF segments (Scheme 3). Central to this strategy was the observation that a hidden symmetry element was present within the macrocyclic core. The functionality and stereochemistry of C_1-C_8 mapped nicely on the C_{18}-C_{25} subunit. The lone exception to this correlation was the presence of the C_4 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 Krause[24] and Gagosz[25] had demonstrated that Au- or Agcatalyzed 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 (Ph_3P, CBr_4, CH_2Cl_2; *n*-BuLi, THF, 69% over 2 steps). Diol deprotection and subsequent esterifications provided the propargyl benzoate **22**. Sonogashira coupling[27] 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 alkynylation[31] 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 $AgBF_4$ (10 mol%) in degassed benzene at 80°C to produce the *trans*-DHF **33** in 65–70% yield on 5-gram 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 silvermediated activation of allene **32** could promote the nucleophilic attack by proximal alcohol moiety to deliver the DHF **33** after protodemetallation. 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**. Protodemetallation followed by Lewis (or Bronsted) acid-activated aromatization would produce the furan **35**.

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 pivaloate (Piv) moiety was problematic. Fortunately, we found that treatment with modulated methyl lithium (MeLi•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 pivaloate deprotected product (≈10%) was observed under these conditions; however, use of MeLi instead of MeLi•LiBr led to significantly larger amount of depivaloated product.

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 MeLi•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 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 improvement[35] 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 HF•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 nucleo-phile.[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 C_8 stereochemistry. Unfortunately, despite considerable efforts using either the major or minor C_8 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, Et_2O, THF / hexanes). Based on these unexpected results, a revised approach was needed to circumvent the iterative formation of the C_8-C_9 and the C_9-C_{10} bonds.

The successful synthesis of the C_1-C_{14} 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 amphidinolide B,[40] the organolithium strategy brought with its potential for metallotropic rearrangement[41] 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 coupling[27] between iodide **11** and TMS-acetylene (**45**) cleanly furnished the enyne **46** in excellent chemical yield. Use of a Pd(II) salts [*e.g.* $(Ph_3P)_2PdCl_2$] gave reduced chemical yields as compared to $(Ph_3P)_4Pd$. Next, Pd(0)-catalyzed hydrostannylation[42] 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 C_8 stereochemistry in a single operation. The C_8 stereochemistry was confirmed by advanced Mosher ester

analysis.[43] After TBS protection at C_8, selective desilylation at C_{14} and conversion to correspondng iodide provided the C_1-C_{14} subunit **9**.

With a viable, unified route to the C_1-C_{14} domain, our attention shifted to construction of the remaining sulfone subunit (Scheme 9). Starting from the common ketone intermediate **20**, borohydride reduction provided corresponding alcohol as a 1.7:1 mixture at C_{22}. 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, pivaloate 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 C_{15} thiophenyl version[45] of **55** proved problematic in our hands. Oxidation generated the C_{18} ketone **58**. As we had done previously,[9a] we planned to mask the C_{18} ketone as ketal **62**. Despite our considerable efforts, we were unable to effect this process. Consequently, it was necessary to develop an alternate method for masking the C_{18} 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 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 C_{18} to help direct lithiation at C_{15} and stabilize any resultant anion.

Based on this speculative C_{18}-chelation hypothesis, we embarked on the synthesis of a fully functionalized C_{15}-C_{29} system containing an appropriately selected protecting group at C_{18} (Scheme 11). We strategically targeted amphidinolide F (**4**) first due to the C_{25} simplified sidearm 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 C_{18} as it is well known to be labile under mildly acidic conditions.[47] Starting from ketone **58**, L-Selectride reduction cleanly provided the 18*S* isomer **56** as determined by advanced Mosher ester analysis.[43] Protection at C_{18} 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 C_{15} sulfone **66**. Selective removal of the C_{25} 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*). C_{24} 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 C_{14}-C_{15} 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 C_{18} chelating protecting group is likely key to the success of both the alkylation and the oxidative desulfurization. Both the C_1 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**, $LiAlH_4$ reduction removed the pivaloate with concomitant reduction of the C_{15} 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 C_{24} TES ether in presence of multiple 2° TBS ethers and a OTHP moiety. Fortunately, mild acidic conditions (PPTS, MeOH) selectively removed the C_{24} TES ether to provide seco acid **75**. We speculated that the sterically congested nature of the C_{18} 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 conditions[49] provided the 25-membered macrolactone **77** in good yield (69% over 2 steps). Yamaguchi macrolactonization conditions[50] 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/H_2O, $MgBr_2$,[51] Me_2AlCl,[52] BF_3•OEt_2/1,2-ethanedithiol[53]) – ultimately leading to decomposition in each case. We speculated that the acid sensitivity of the macrocycle **77** was due to preferential ionization at C_{24}, which would generate a highly stabilized dienyl cation.

Despite this significant setback to our campaign towards 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/H_2O or PPTS/MeOH[54] did not decompose the macrocycle (nor was any appreciable deprotection of the C_{18} OTHP observed). We hypothesized if we could identify a more acid labile protecting group at C_{18} 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 (circa 250 times in one study)[47] while maintaining the necessary chelating ability for the sulfone alkylation / oxidative desulfurization sequence.

The successful execution of this C_{18} 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 (C_{15} debenzylation) proved problematic under our prior Pd/C, H_2 conditions (see Supporting Information). Use of the Freeman reagent[55] 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 conditions[50] 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 C_{18} deprotection. We were thrilled to find that our OEE hypothesis proved valid as aqueous acetic acid conditions smoothly provided the corresponding C_{18} alcohol **78**. This alcohol **78** existed as a mixture of the hydroxyl ketone and C_{15} hemiketal; however, the equilibrium could be driven to the C_{15}, C_{18} 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., TASF[56]); however, prolonged exposure to Et_3N•3HF[57] ultimately proved to be effective – yielding am-phidinolide F (**4**) in 56% isolated yield. Spectral comparison of synthetic amphidinolide F was in good agreement with the spectral data (^1H, ^{13}C, $[\alpha]_D$) reported by Kobayashi and coworkers. It should be noted that both Kobayashi[58] 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 $CDCl_3$) 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**, am-phidinolide 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 C_1-C_{14} 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 alkynylation[60] with commercially available alkyne **90** gave the desired propargyl alcohol **92** in high yield and enantioselectivity (Scheme 14). After silyl protection at C_{29}, cuprate addition to the alkynoate **93** generated the desired *E*-alkene **94** in complete stereoselectivity. $LiAlH_4$ reduction produced the allyl alcohol **95** in 89% yield over two steps. This compound was employed to determine the absolute configuration at C_{29} by desilylation (TBAF) and advanced Mosher ester analysis.[43] Conversion of alcohol **95** to the corresponding tributylphosphonium salt **96** was accomplished by treatment with CBr_4, Ph_3P followed by displacement with PBu_3 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 C_{15}-C_{34} sulfone **99** is shown in Scheme 15. Starting from previously made bis-TBS ether **80**, TBAF mediated desilylation followed by bis-TES protection produced **97**. Next, tandem C_{25} 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 C_{14}-C_{15} 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 C_{24} TES ether generated the seco acid. Yamaguchi macrolactonization produced the 25-membered macrolactone **105** in 63% yield over two steps. Aqueous acetic acid conditions again proved effective for selective removal of the C_{18} OEE moiety. Subsequent oxidation using DMP yielded tetra-TBS protected amphidinolide C. Gratifyingly, global deprotection using Et_3N•3HF produced the natural product **1**, which was matched nicely with the observed spectra (^1H, ^{13}C NMR in C_6D_6).[12b–c] Additionally, the optical rotation data was in agreement with the literature value [Synthetic: $[\alpha]_D^{23}$ = −98.5° (*c* = 0.21, $CHCl_3$); Natural:[12] $[\alpha]_D^{26}$ = −106° (*c* = 1.0, $CHCl_3$)]. 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 C_9-C_{11} diene and established the C_8 stereocenter in single operation. An efficient 6-step sequence provided access to the C_{26}-C_{34} aphidinolide C subunit and the Tamura-Vedejs olefination incorporated the C_{25}-C_{29} sidearm of amphidinolide F and the C_{25}-C_{34} sidearm of amphidinolide C. A sterically congested sulfone alkylation / oxidative desulfurization sequence was utilized to couple the major subunits and incorporate the C_{15} ketone. The presence of chelating moiety at C_{18} was critical to the success of the oxidative desulfurization step. A carefully orchestrated sequence for stepwise revealing of the C_{24} alcohol followed by macrolactonization, C_{18} deprotection and oxidation provided access to the protected amphidinolide natural products. The final global deprotection was uniquely feasible utilizing Et_3N•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 C_{25} sidearm on biological activity. These studies will be reported in due course.

Supplementary Material

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REFERENCES

1. Brachmachari, G. Bioactive Natural Products. Brachmachari, G., editor. Hackensack, NJ: World Scientific Publishing; 2011. p. 1-199.
2. (a) Nicolaou, KC.; Sorensen, JE., editors. Classics in Total Synthesis: Targets, Strategies, Methods. New York: Wiley-VCH; 1996. (b) Wilson RM, Danishefsky SJ. J. Org. Chem. 2006; 71:8329–8351. [PubMed: 17064003] (c) Cossy, J.; Arseniyadis, S., editors. Modern Tools for the Synthesis of Complex Bioactive Molecules. John Wiley and Sons; 2012.
3. Kinghorn, AD.; Falk, H.; Kobayashi, J., editors. The Epothilones: An Outstanding Family of Anti-Tumor Agents. From Soil to the Clinic. NewYork, NY, USA: SpringerWien; 2009.
4. Daniel PT, Koert U, Schuppan J. Angew. Chem. Int. Ed. 2006; 45:872–893.
5. Hale KJ, Manaviazar S. Chem. Asian. J. 2010; 5:704–754. [PubMed: 20354984]
6. (a) Ishibashi M, Kobayashi J. Heterocycles. 1997; 44:543–572.(b) Chakraborty TK, Das S. Curr. Med. Chem. Anti-cancer Agents. 2001; 1:131–149.(c) Kobayashi J, Shimbo K, Kubota T, Tsuda M. Pur. App. Chem. 2003; 75:337–342.(d) Kobayashi J, Tsuda M. Nat. Prod. Rep. 2004; 21:77–93. [PubMed: 15039836] (e) Colby EA, Jamison TF. Org. Biomol. Chem. 2005; 3:2675–2684. [PubMed: 16032344] (f) Kobayashi J, Kubota T. J. Nat. Prod. 2007; 70:451–460. [PubMed:

17335244] (g) Hiersemann N, Kobayashi J. J. Antibiot. 2008; 61:271–284. [PubMed: 18653992] (h) Fürstner A. Israel J. Chem. 2011; 51:329–345.

7. (a) Williams D, Kissel WS. J. Am. Chem. Soc. 1988; 120:11198–11199.(b) Williams DR, Meyer BJ, Mi L. Org. Lett. 2000; 2:945–948. [PubMed: 10768193] (c) Williams DR, Meyer KG. J. Am. Chem. Soc. 2001; 123:765–766. [PubMed: 11456603] (d) Angew. Chem. Int. Ed. 2002; 41:508–511.(e) Maleczka RE, Terrell LR Jr, Geng F, Ward JS III. Org. Lett. 2002; 4:2841–2844. [PubMed: 12182569] (f) Fürstner A, Aissa C, Riveiros R, Ragot J. Angew. Chem. Int. Ed. 2002; 41:4763–4766.(g) Trost BM, Chisholm JD, Wrobleski SJ, Jung M. J. Am. Chem. Soc. 2002; 124:12420–12421. [PubMed: 12381177] (h) Aiessa C, Riveiros R, Ragot J, Fürstner A. J. Am. Chem. Soc. 2003; 125:15512–15520. [PubMed: 14664598] (i) Ghosh AK, Liu C. J. Am. Chem. Soc. 2003; 125:2374–2375. [PubMed: 12603108] (j) Lepage O, Kattnig E, Fürstner A. J. Am. Chem. Soc. 2004; 126:15970–15971. [PubMed: 15584724] (k) Ghosh AK, Gong G. J. Am. Chem. Soc. 2004; 126:3704–3705. [PubMed: 15038710] (l) Trost BM, Harrington PE. J. Am. Chem. Soc. 2004; 126:5028–5029. [PubMed: 15099060] (m) Trost BM, Papillion JPN. J. Am. Chem. Soc. 2004; 126:13618–13619. [PubMed: 15493910] (n) Trost BM, Wrobleski ST, Chisholm JD, Harrington PE, Jung M. J. Am. Chem. Soc. 2005; 127:13589–13597. [PubMed: 16190724] (o) Harrington PE, Chisholm JD, Wrobleski ST. J. Am. Chem. Soc. 2005; 127:13598–13610. [PubMed: 16190725] (p) Colby EA, O'Brien KC, Jamison TF. J. Am. Chem. Soc. 2005; 127:4297–4307. [PubMed: 15783211] (q) Trost BM, Papillon JPN, Nussbaumer T. J. Am. Chem. Soc. 2005; 127:17921–17937. [PubMed: 16351124] (r) Va P, Roush WR. J. Am. Chem. Soc. 2006; 128:15960–15961. [PubMed: 17165709] (s) Kim CH, An HJ, Shin WK, Yu W, Woo SK, Jung SK, Lee E. Angew. Chem. Int. Ed. 2006; 45:8019–8021.(t) Ghosh AK, Gong G. J. Org. Chem. 2006; 71:1085–1093. [PubMed: 16438525] (u) Fürstner A, Kattnig E, Lepage O. J. Am. Chem. Soc. 2006; 128:9194–9204. [PubMed: 16834393] (v) Nicoloau KC, Brenzovich WE, Bulger PG, Francis TM. Org. Biomol. Chem. 2006; 4:2119–2157. [PubMed: 16729126] (w) Nicolaou KC, Bulger PG, Brenzovich WE. Org. Biomol. Chem. 2006; 4:2158–2183. [PubMed: 16729127] (x) Deng L-S, Huang X-P, Zhao G. J. Org. Chem. 2006; 71:4625–4635. [PubMed: 16749797] (y) Jin J, Chen Y, Li Y, Wu J, Dai W-M. Org. Lett. 2007; 9:2585–2588. [PubMed: 17536814] (z) Va P, Roush WR. Tetrahedron. 2007; 63:5768–5796. [PubMed: 18575572] (aa) Fürstner A, Bouchez LC, Funel J-A, Liepins V, Poree F-H, Gilmour R, Beaufils F, Laurich D, Tamiya M. Angew. Chem. Int. Ed. 2007; 46:9265–9270.(bb) Dai W-M, Chen Y, Jin J, Wu J, Lou J, He Q. Synlett. 2008:1737–1741.(cc) Barbazanges M, Meyer C, Cossy J. Org. Lett. 2008; 10:4489–4492. [PubMed: 18811171] (dd) Kim CH, An HJ, Shin WK, Yu W, Woo SK, Jung SK, Lee E. Chem. Asian. J. 2008; 3:1523–1534. [PubMed: 18604821] (ee) Rodriquez-Escrich C, Urpi F, Vilarrasa J. Org. Lett. 2008; 10:5191–5194. [PubMed: 18928293] (ff) Lu L, Zhang W, Carter RG. J. Am. Chem. Soc. 2008; 130:7253–7255. [PubMed: 18489095] (gg) Lu L, Zhang W, Carter RG. J. Am. Chem. Soc. 2008; 130:11834.(hh) Fürstner A, Bouchez LC, Morency L, Funel J-A, Liepins V, Poree F-H, Gilmour R, Lau-rich D, Beaufils F, Tamiya M. Chem. Eur. J. 2009; 15:3983–4010. [PubMed: 19241433] (ii) Hangyou M, Ishiyama H, Takahashi Y, Kobayashi J. Org. Lett. 2009; 11:5046–5049. [PubMed: 19803529] (jj) Ko HM, Lee CW, Kwon HK, Chung HS, Choi SY, Chung YK, Lee E. Angew. Chem. Int. Ed. 2009; 47:2364–2366.(kk) Fürstner A, Flügge S, Larionov O, Takahashi Y, Kubota T, Kobayashi J. Chem. Eur. J. 2009; 15:4011–4029. [PubMed: 19241434] (ll) Yadav JS, Reddy CS. Org. Lett. 2009; 11:1705–1708. [PubMed: 19323491] (jj) Li H, Wu J, Luo J, Dai W-M. Chem. Eur. J. 2010; 16:11530–11534. [PubMed: 20803588] (ll) Wu D, Li H, Jin J, Wu J, Dai W-M. Synlett. 2011:895–898.(mm) Sun L, Wu D, Wu J, Dai W-M. Synlett. 2011:3036–3040.(nn) Hara A, Morimoto R, Iwasaki Y, Saitoh T, Ishikara Y, Nishiyama S. Angew. Chem. Int. Ed. 2012; 51:9877–9880.(oo) Lu L, Zhang W, Nam S, Horne DA, Jove R, Carter RG. J. Org. Chem. 2013; 78:2213–2247. [PubMed: 23406192] (pp) Williams DR, Myers BJ, Mi L. Org. Lett. 2013; 15:2070.(qq) Williams DR, Myers BJ, Mi L, Binder RJ. J. Org. Chem. 2013; 78:4762–4778. [PubMed: 23590535] (rr) Volchkov I, Lee D. J. Am. Chem. Soc. 2013; 135:5324–5427. [PubMed: 23514007]
8. (a) Ishiyama H, Ishibashi M, Kobayashi J. Chem. Pharm. Bull. 1996; 44:1819–1822.(b) Kubota T, Tsuda M, Kobayashi J. Tetrahedron. 2003; 59:1613–1625.(c) Shotwell JB, Roush WR. Org. Lett. 2004; 12:3865–3868. [PubMed: 15469369] (d) Mohapatra DK, Rahaman H, Chorghade MS, Gurjar MK. Synlett. 2007:567–570.(e) Bates RH, Shotwell JB, Roush WR. Org. Lett. 2008; 9:4343–4346. [PubMed: 18783230] (f) Armstrong A, Pyrkotis C. Tetrahedron Lett. 2009; 50:3325–3328.(g) Paudyal MP, Rath NP, Spilling CD. Org. Lett. 2010; 12:2954–2957. [PubMed: 20527780] (h) Ferri L, Figadre B. Org. Lett. 2010; 12:4976–4979. [PubMed: 20882983] (i) Roy S, Spilling CD. Org.

Lett. 2010; 12:5326–5329. [PubMed: 21028791] (j) Morra NA, Pagenkopf BL. Org. Lett. 2011; 13:572–575. [PubMed: 21254755] Fischer, DA.; Williams, DR.; De, R.; Fultz, M.; Morales-Ramos, A.; Rodriguez-Reyes, D. San Diego, CA. 243st National American Chemical Society Meeting; March 25–29 2012; ORGN-756(l) Wu D, Forsyth CJ. Org. Lett. 2013; 15:1178–1181. [PubMed: 23441846] (m) Clark JS, Yang G, Osnowski AP. Org. Lett. 2013; 15:1460–1463. [PubMed: 23527702] (n) Clark JS, Yang G, Osnowski AP. Org. Lett. 2013; 15:1464–1467. [PubMed: 23527614]

9. (a) Mahapatra S, Carter RG. Org. Biomol. Chem. 2009; 7:4582–4585. [PubMed: 19865690] Mahapatra, S.; Carter, RG. Anaheim, CA. 241st National American Chemical Society Meeting; March 27–31, 2011; 2011. ORGN-295Mahapatra, S.; Carter, RG. Portland, OR. Northwest Regional American Chemical Society Meeting; June 26–30, 2011; NORM-261
10. Mahapatra S, Carter RG. Angew. Chem., Int. Ed. 2012; 51:7948–7951.
11. Fürstner and co-orkers have recently completed an elegant total synthesis of amphidinolide F:Valot G, Regens CS, O'Malley DP, Godineau E, Takikawa H, Fürstner A. Angew. Chem. Int. Ed. Early View.
12. (a) Kobayashi J, Ishibashi M, Wälchli NR, Nakamura H, Yamasu T, Hirata Y, Sasaki T, Ohizumi Y. J. Am. Chem. Soc. 1988; 110:490–494.(b) Kubota T, Tsuda M, Kobayashi J. Org. Lett. 2001; 3:1363–1366. [PubMed: 11348235] (c) Kubota T, Tsuda M, Kobayashi J. Tetrahedron. 2001; 57:5975–5977.(d) Kubota T, Tsuda M, Kobayashi J. Tetrahedron. 2003; 59:1613–1625.
13. (a) Kubota T, Sakuma Y, Tsuda M, Kobayashi J. Mar. Drugs. 2004; 2:83–87.(b) Kubota T, Suzuki A, Yamada M, Baba S, Kobayashi J. Heterocycles. 2010; 82:333–338.
14. Tsuda M, Endo T, Kobayashi J. Tetrahedron. 1999; 55:14565–14570.
15. Kobayashi J, Tsuda M, Ishibashi M, Shigemori H, Yamasu T, Hirota H, Sasaki T. J. Antibiot. 1991; 44:1259–1261. [PubMed: 1761423]
16. Zhou X-T, Carter RG. Angew. Chem. Int. Ed. 2006; 45:1787–1790.
17. Fuwa H, Okamura Y, Natsugari H. Tetrahedron. 2004; 60:5341–5532.
18. (a) Little RD, Myong SO. Tetrahedron Lett. 1980; 21:3339–3342.(b) Hwu JR. J. Org. Chem. 1983; 48:4432–4433.(c) Yamada S, Nakayama K, Takayama H. Tetrahedron Lett. 1984; 25:3239–3242. (d) Bonaparte AC, Betush MP, Panseri BM, Mastarone DJ, Murphy RK, Murphree SS. Org. Lett. 2011; 13:1447–1449. [PubMed: 21319833]
19. (a) Paquette LA, Barriault L, Pissarnitski D. J. Am. Chem. Soc. 1999; 121:4542–4543.(b) Arjona O, Menchaca R, Plumet J. Org. Lett. 2001; 3:107–109. [PubMed: 11429849]
20. Smith AB, Adams CM III. Acc. Chem. Res. 2004; 37:365–377. [PubMed: 15196046]
21. Menche D, Hassfeld J, Li J, Rudolph S. J. Am. Chem. Soc. 1996; 129:6100–6101. [PubMed: 17455939] See also: Harris H, Jarowicki K, Kocienski P, Bell R. Synlett. 1996:903–905. Hanisch I, Bruckner R. Synlett. 2006:374–378. Yin N, Wang G, Qian M, Negishi E. Angew. Chem., Int. Ed. 2006; 45:2916–2920.
22. (a) Katsuki T, Sharpless KB. J. Am. Chem. Soc. 1980; 102:5974–5976.(b) Gao Y, Klunder JM, Hanson RM, Masamune H, Ko SY, Sharpless KB. J. Am. Chem. Soc. 1987; 109:5765–5780.(C) Schomaker JM, Pul-gam VR, Borhan B. J. Am. Chem. Soc. 2004; 126:13600–13601. [PubMed: 15493901]
23. Shanmugam P, Miyashita M. Org. Lett. 2003; 5:3265–3268. [PubMed: 12943403]
24. (a) Hoffmann-Röder A, Krause N. Org. Lett. 2001; 3:2537–2538. [PubMed: 11483054] (b) Volz F, Krause N. Org. Biomol. Chem. 2007; 5:1519–1521. [PubMed: 17571178]
25. Buzas A, Istrate F, Gagosz F. Org. Lett. 2006; 8:1957–1759. [PubMed: 16623594]
26. (a) Flögel O, Amombo MGO, Reiβig H-U, Zahn G, Brüdgam I, Hartl H. Chem. Eur. J. 2003; 9:1405–1415. [PubMed: 12645030] (b) Herradon B. Tetrahedron: Asymm. 1991; 2:191–194.
27. Sonogashira K, Tohda Y, Hagihara N. Tetrahedron Lett. 1975; 16:4467–4470.
28. Gagnon D, Lauzon S, Godbout C, Spino C. Org. Lett. 2005; 7:4769–4771. [PubMed: 16209531]
29. Judd WR, Ban S, Aubé J. J. Am. Chem. Soc. 2006; 128:13736–13741. [PubMed: 17044701]
30. Mapp AK, Heathcock CH. J. Org. Chem. 1999; 64:23–27. [PubMed: 11674080]
31. Boyall D, López F, Sasaki H, Frantz D, Carreira EM. Org. Lett. 2001; 2:4233–4236. [PubMed: 11150207]

32. Kolb HC, Van Nieuwenhze MS, Sharpless KB. Chem. Rev. 1994; 94:2483–2547.
33. Carter RG, Weldon DJ. Org. Lett. 2000; 2:3913–3916. [PubMed: 11101452]
34. (a) Turks M, Fairweather KA, Scopelliti R, Vogel P. Eur. J. Org. Chem. 2011:3317–3328.(b) Exner CJ, Turks M, Fonquerne F, Vogel P. Chem. Eur. J. 2011; 17:4246–4253. [PubMed: 21387431] (c) Exner CJ, Lalcef S, Poli F, Turks M, Vogel P. J. Org. Chem. 2011; 76:840–845. [PubMed: 21218837]
35. Furrow ME, Myers AG. J. Am. Chem. Soc. 2004; 126:5436–5445. [PubMed: 15113215]
36. Barton DHR, McCombie SW. J. Chem. Soc., Perkin Trans. 1975; 1:1574–1585.
37. Please note that **41** was converted to a known degradation intermediate of amphidinolide C.[12d] See supporting information for full details.
38. Nemoto H, Ma R, Moriguchi H, Kawamura T, Kamiya M, Shibuya M. J. Org. Chem. 2007; 72:9850–9853. [PubMed: 17988149]
39. Nemoto H, Kawamura T, Miyoshi N. J. Am. Chem. Soc. 2005; 127:14546–14547. [PubMed: 16231887]
40. Mandal AK, Schneekloth JS Jr, Kuramochi K, Crews CM. Org. Lett. 2006; 8:427–430. [PubMed: 16435851]
41. Hoffmann RW, Polachowski A. Chem. Eur. J. 1998; 4:1724–1730.
42. This reactivity was initially noted by Smith and coworkers as an unwanted side reaction in their synthesis of rapamycin. Smith AB III, Condon SM, McCauley JA, Leazer JL Jr, Leahy JW, Maleczka RE Jr. J. Am. Chem. Soc. 1990; 119:962–973. For alternative routes to similar stannane, see: Oehlschager AC, Hutzinger MW, Aksela R, Sharma S, Singh SM. Tetrahedron Lett. 1990; 31:165–168. Suzenet F, Blart E, Quintard J-P. Synlett. 1998:879–881.
43. Ohtani I, Kusumi T, Kashman Y, Kakisawa H. J. Am. Chem. Soc. 1991; 113:4092–4096.
44. (a) White JD, Kawaski M. J. Org. Chem. 1992; 57:5292–5300.(b) Vong BG, Abraham S, Xiang AX, Theodorakis EA. Org. Lett. 2003; 5:1617–1620. [PubMed: 12735735] (c) Kopecky DJ, Rychnovsky SD. J. Am. Chem. Soc. 2001; 123:8420–8421. [PubMed: 11516301]
45. Kabalka GW, Gooch EE, Sastry KAR. J. Nuc. Med. 1981; 22:908–912.
46. See supporting information for details on this coupling reaction.
47. Greene, TW.; Wuts, PGM, 3rd. Protective Groups in Organic Synthesis. New York: John Wiley & Sons, Inc.; 1999. chapter 2
48. (a) Tamura R, Saegusa K, Kakihana M, Oda D. J. Org. Chem. 1998; 53:2723–2728.(b) Wang Y, Panagabko C, Atkinson J. Bioorg. Med. Chem. 2010; 18:777–786. [PubMed: 20006517] (c) Vedejs E, Marth CF, Ruggeri R. J. Am. Chem. Soc. 1998; 110:3940–3948.
49. Shiina I, Kubota M, Oshiumi H, Hashizume M. J. Org. Chem. 2004; 69:1822–1830. [PubMed: 15058924]
50. Inanaga J, Hirata K, Saeki H, Katsuki T, Yamaguchi M. Bull. Chem. Soc. Jpn. 1979; 52:1989–1993.
51. Kim S, Park JH. Tetrahedron Lett. 1987; 28:439–440.
52. Ogawa Y, Shibasaki M. Tetrahedron Lett. 1984; 25:663–664.
53. Nambiar KP, Mitra A. Tetrahedron Lett. 1994; 35:3033–3036.
54. Miyashita M, Yoshikoshi A, Grieco PA. J. Org. Chem. 1977; 42:3772–3774.
55. Freeman PK, Hutchinson LL. J. Org. Chem. 1980; 45:1924–1930.
56. For TASF mediated desilylation in amphidinolide B synthesis, see Reference 7ff and 7hh.
57. (a) Pirrung MC, Shuey SW, Lever DC, Fallon L. Bioorg. Med. Chem. Lett. 1994; 4:1345–1346.(b) Dunetz JR, Julian LD, Newcom JS, Roush WR. J. Am. Chem. Soc. 2008; 130:16407–16416. [PubMed: 18980317] (c) Hanessian S, Schroeder BR, Giacometti RB, Merner BL, Østergaard M, Swayze EE, Seth PP. Angew. Chem. Int. Ed. 2012; 51:11242–11245.
58. Kubota T, Kobayashi J. Personal Communication.
59. Ragoussis V, Giannikopoulos A, Skoka E, Grivas P. J. Agric. Food. Chem. 2007; 55:5050–5052. [PubMed: 17530861]
60. Trost BM, Weiss AH, Wangelin AK-V. J. Am. Chem. Soc. 2006; 128:8–9. [PubMed: 16390095]

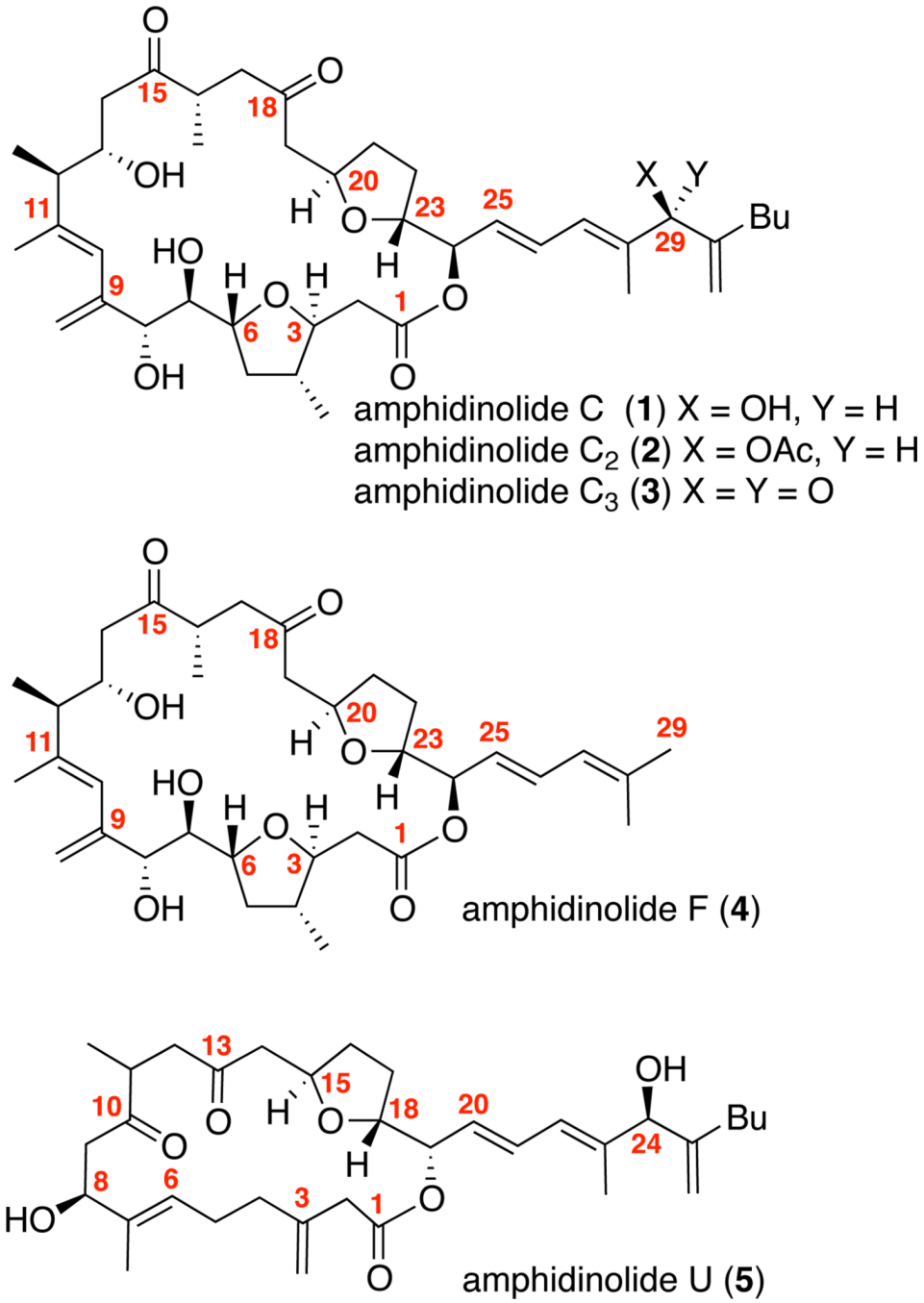
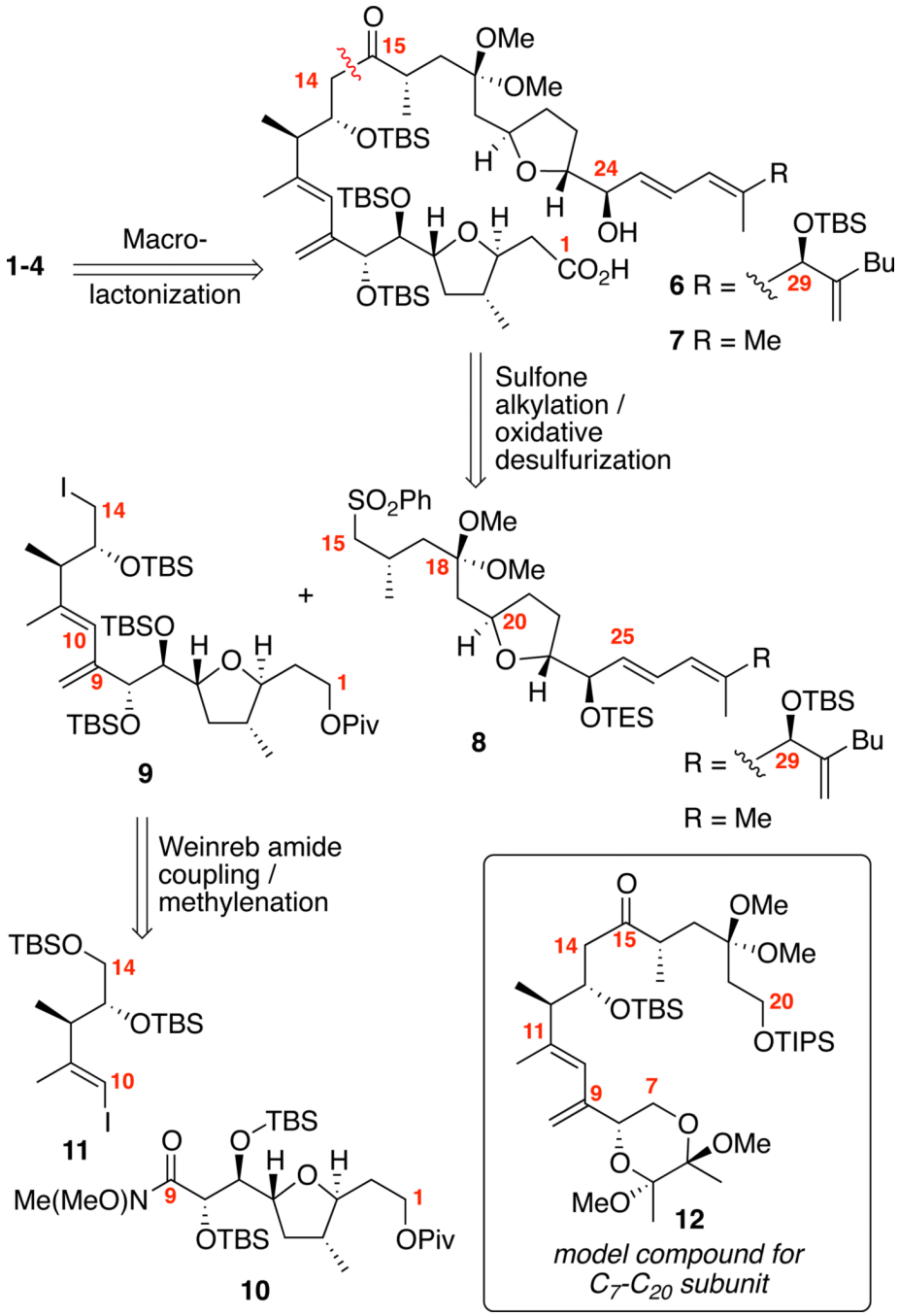
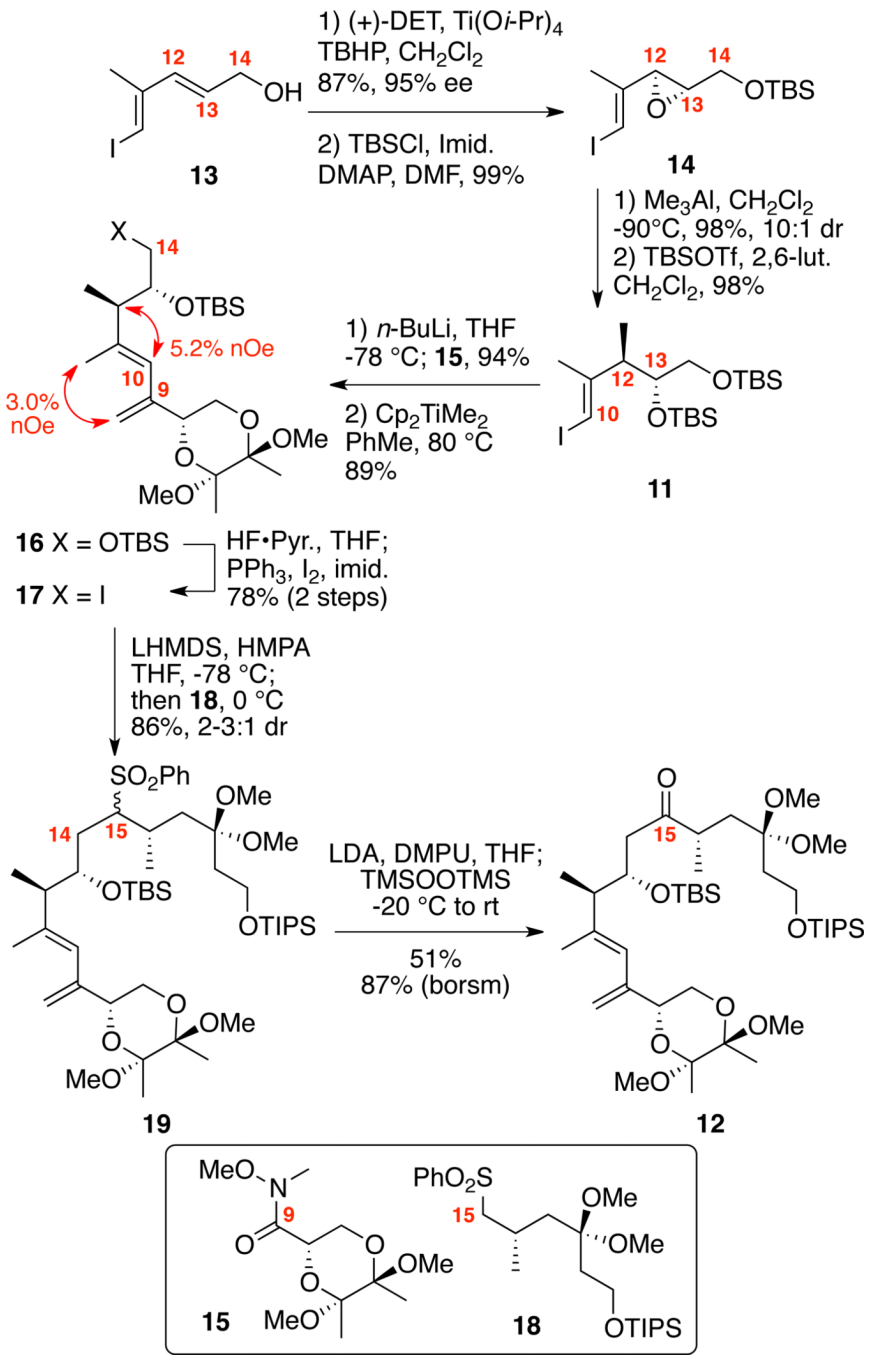


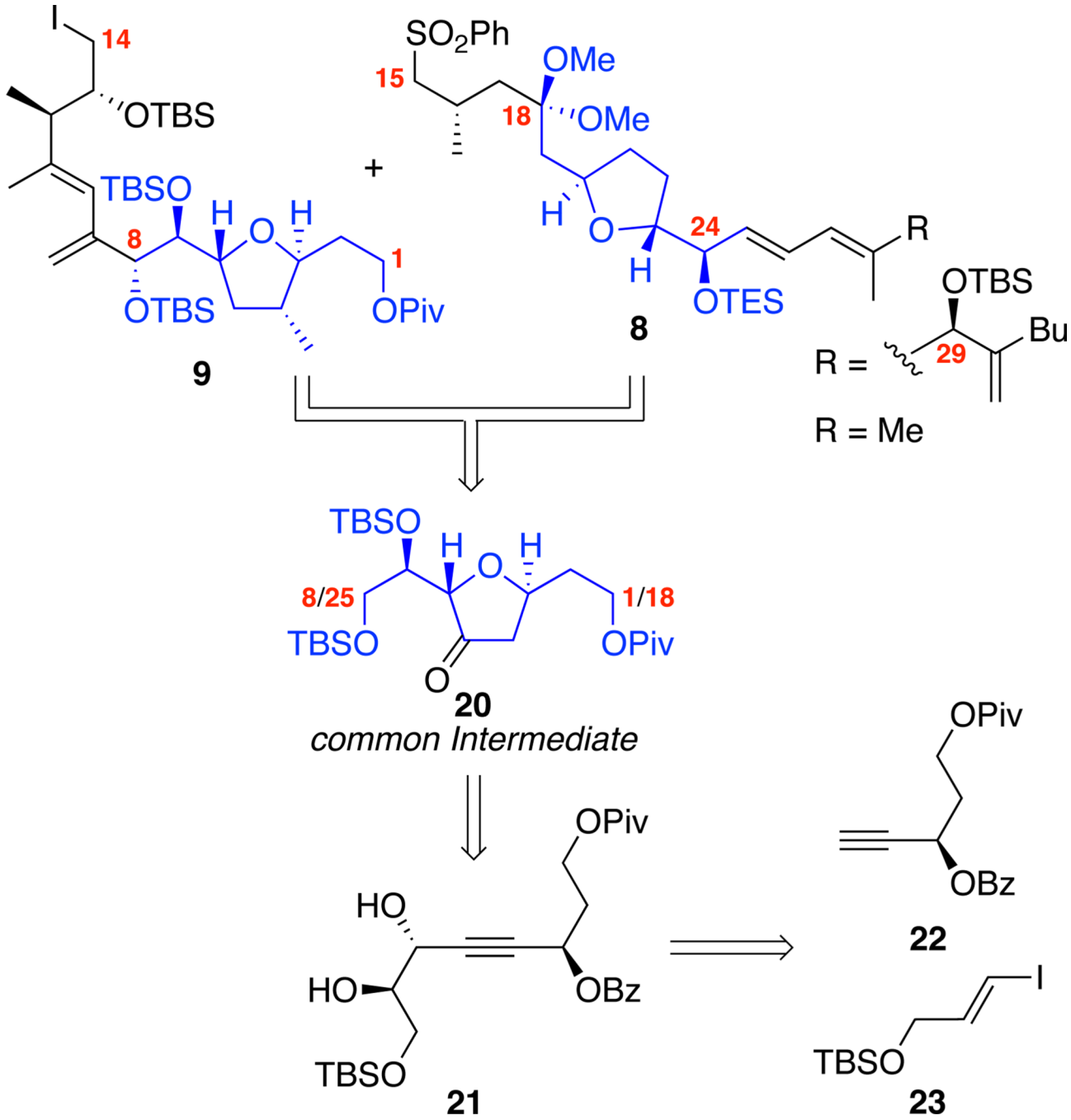
Figure 1.
Amphidinolides C, F and U.



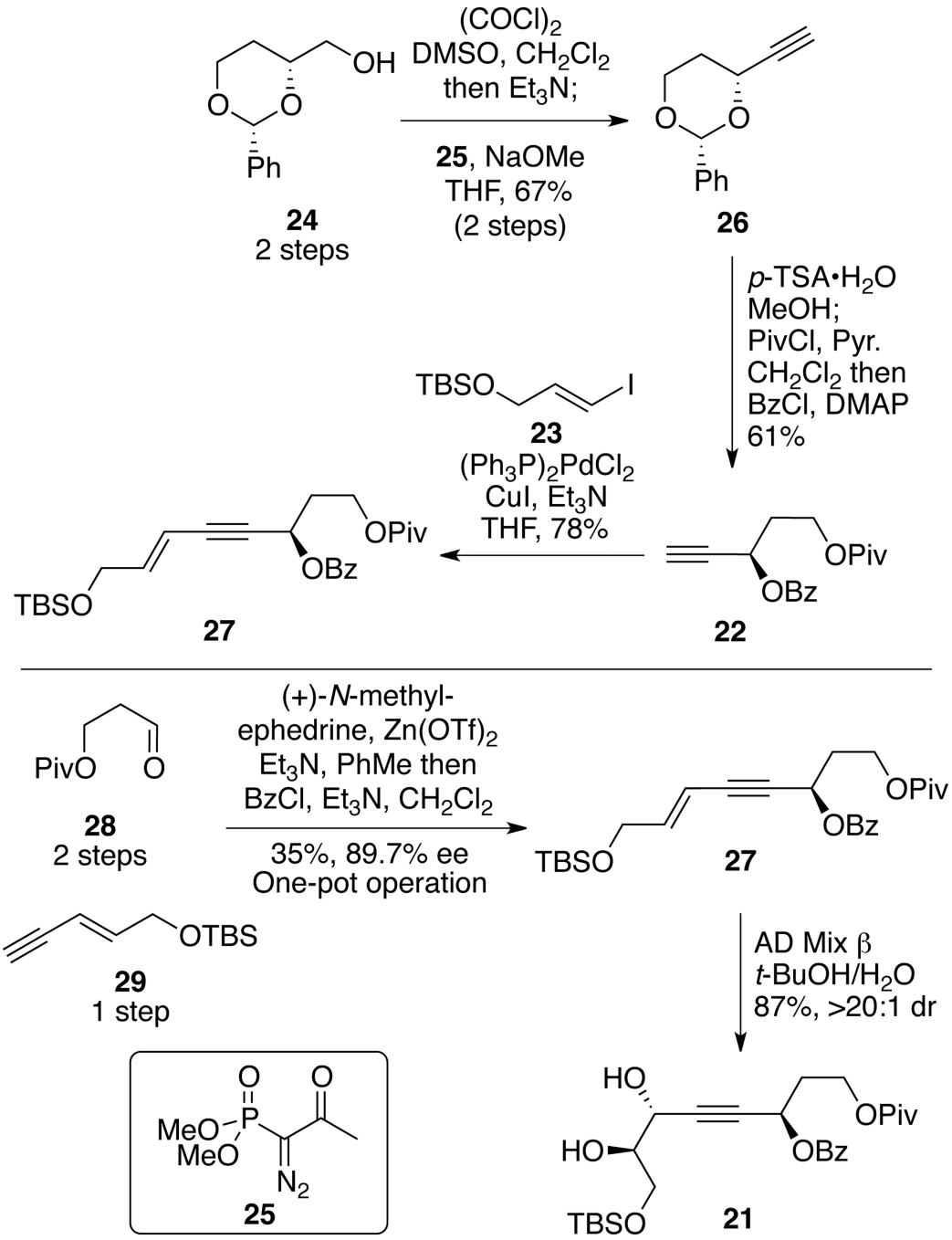
Scheme 1.
Retrosyntheses for Amphidinolides C-C_3 and F.



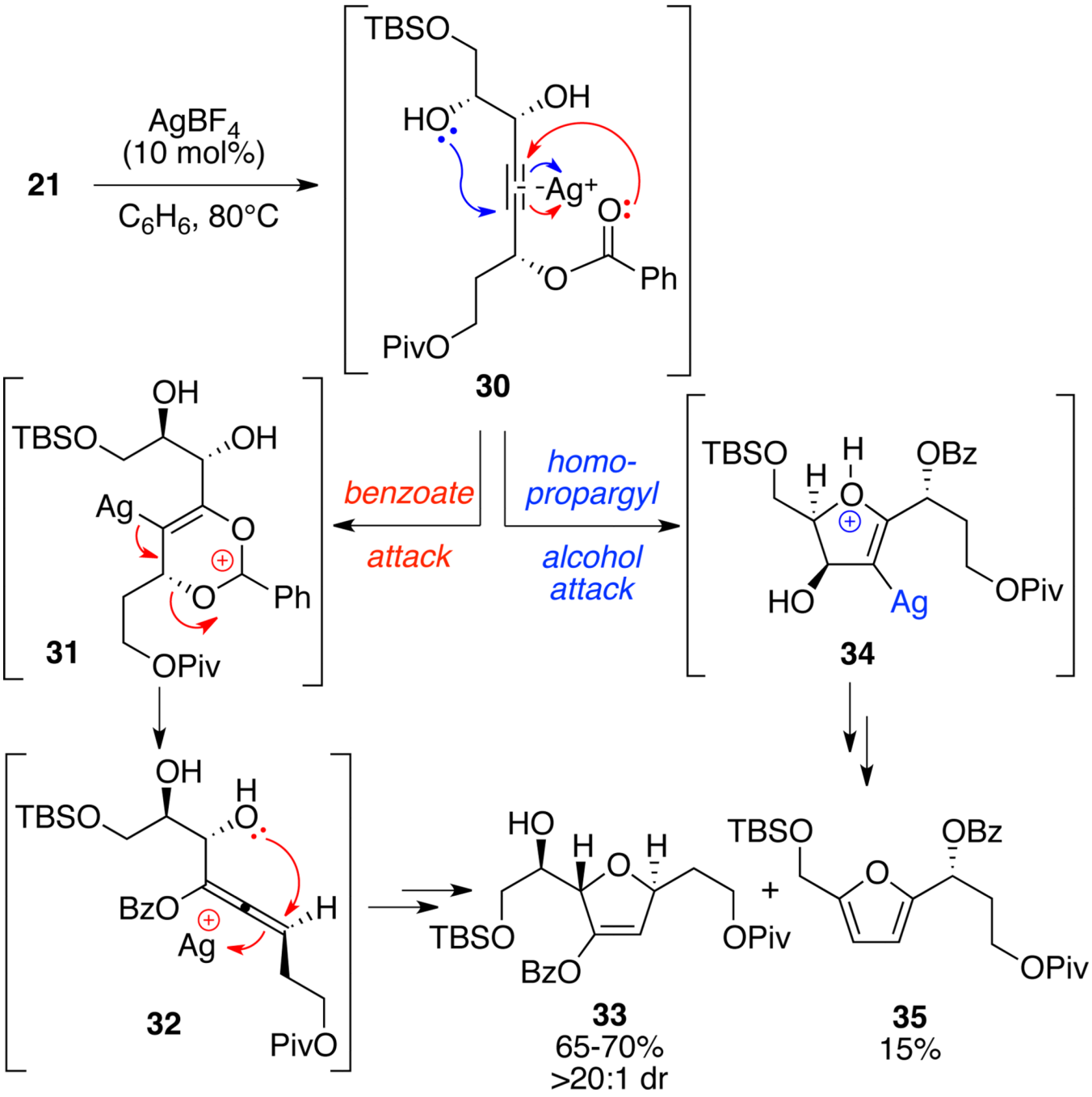
Scheme 2.
Synthesis of C_7-C_{20} Segment: A Model Study.



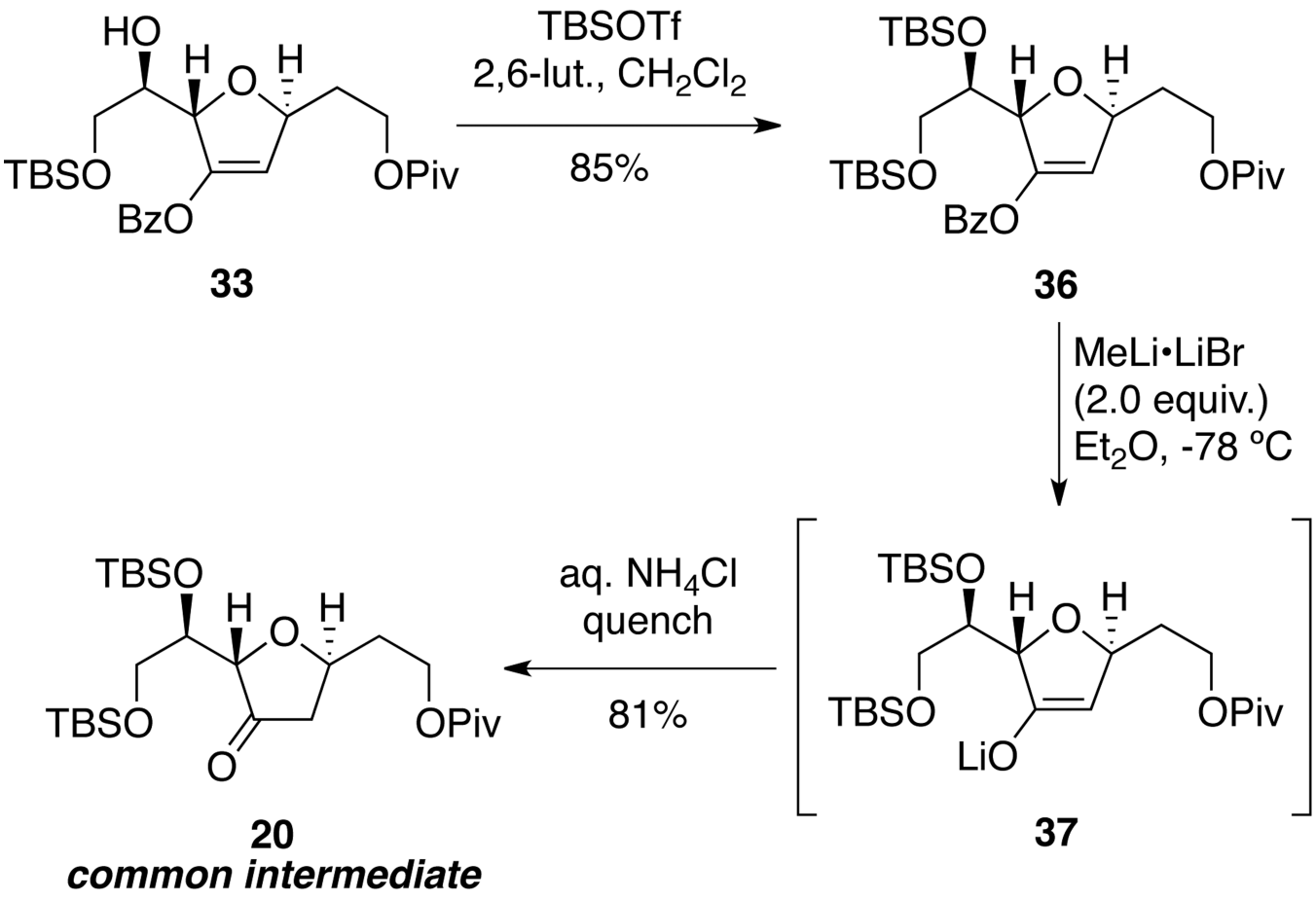
Scheme 3.
Common Intermediate Approach to Major Subunits.



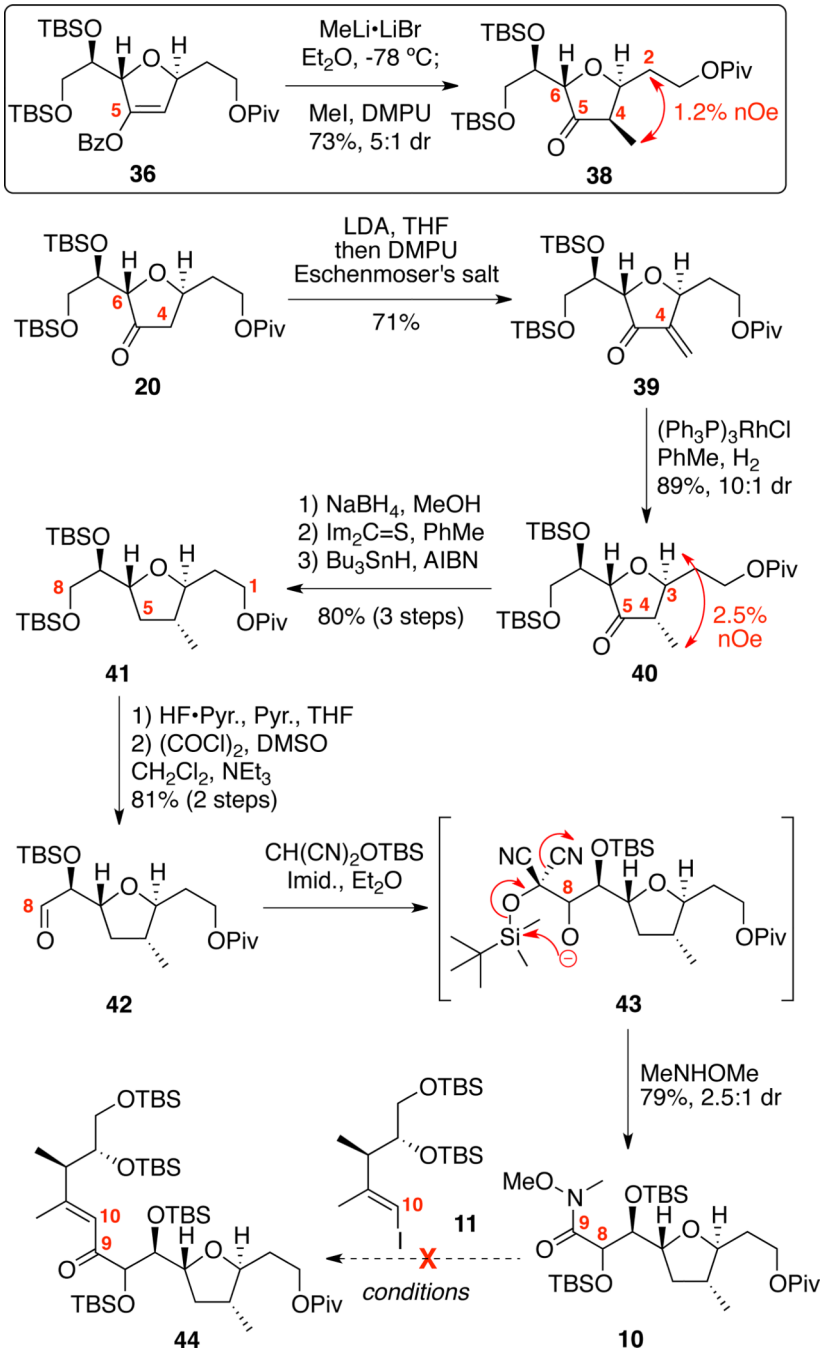
Scheme 4.
Synthesis of Cyclization Precursor.



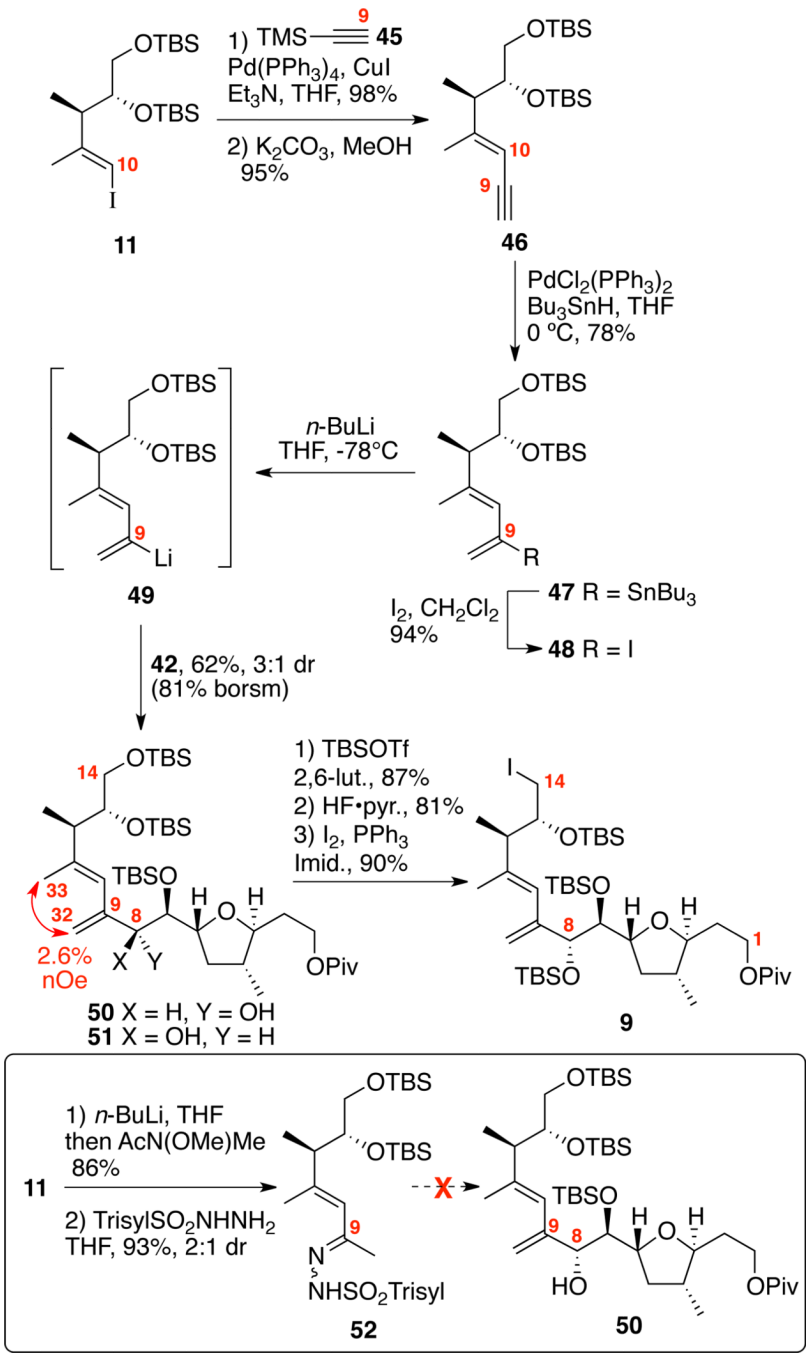
Scheme 5.
Silver-Catalyzed Cyclization to Dihydrofuran.



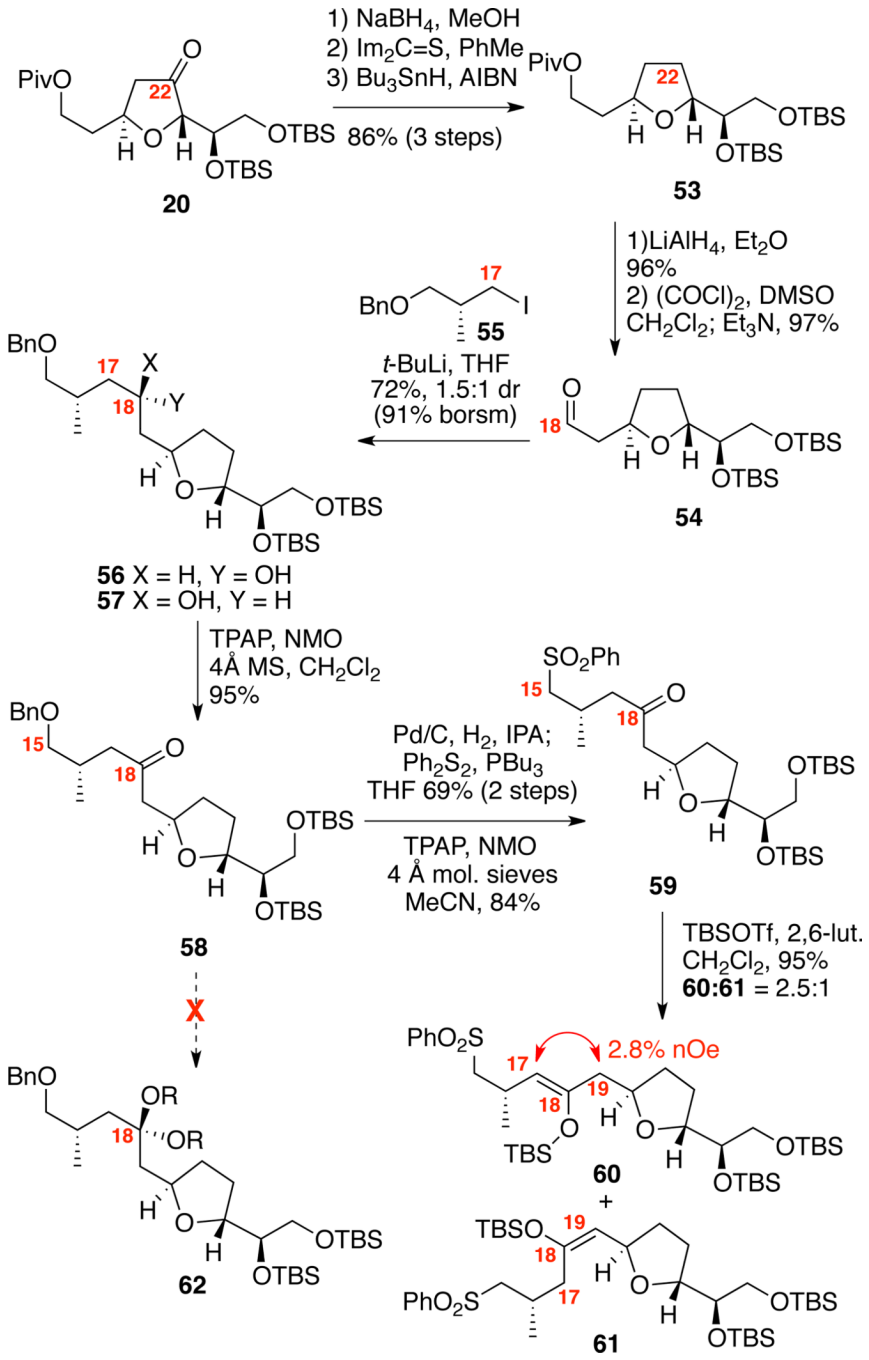
Scheme 6.
Synthesis of the Common Intermediate.



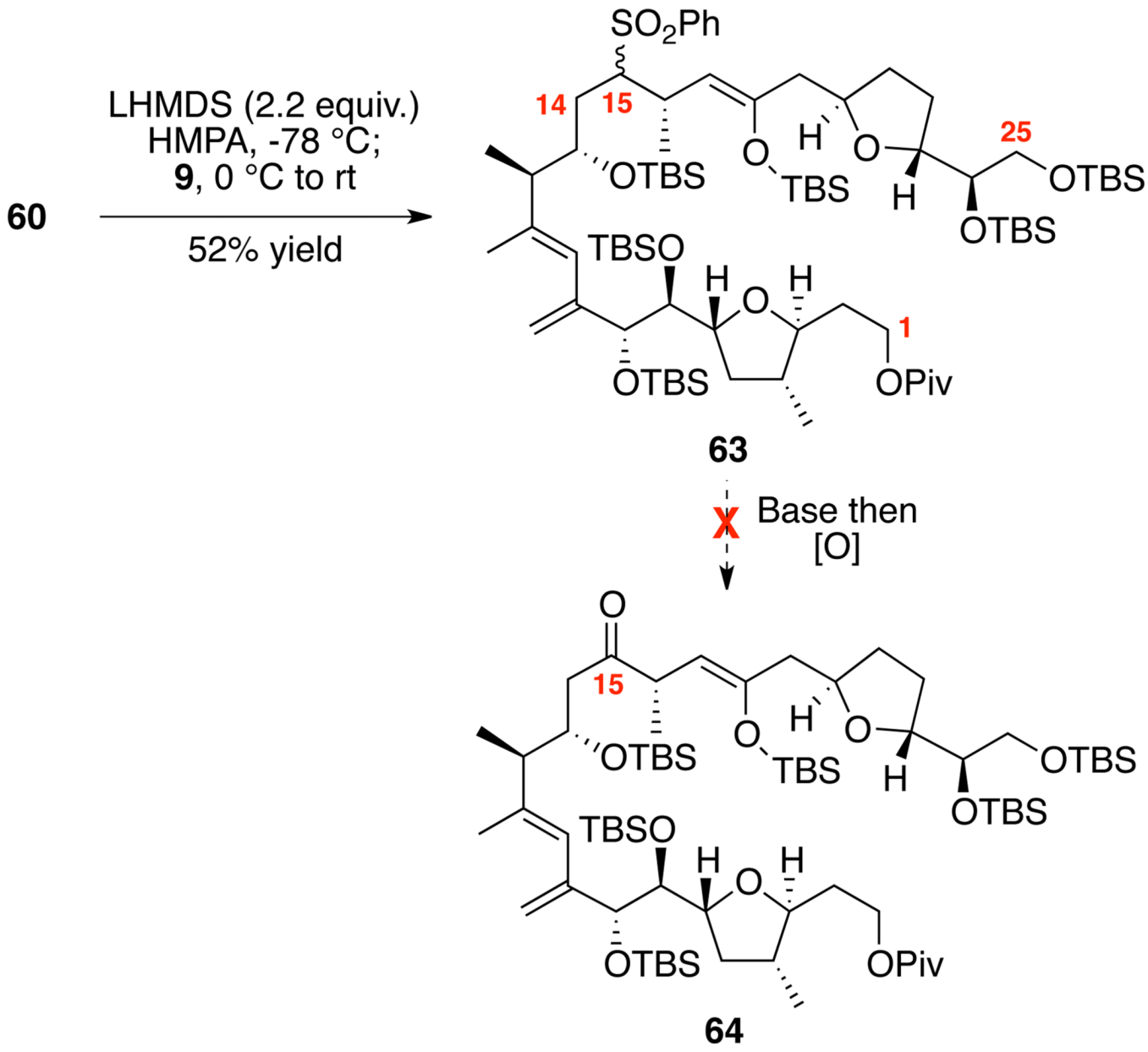
Scheme 7.
Initial Route for C_1-C_{14} Subunit.



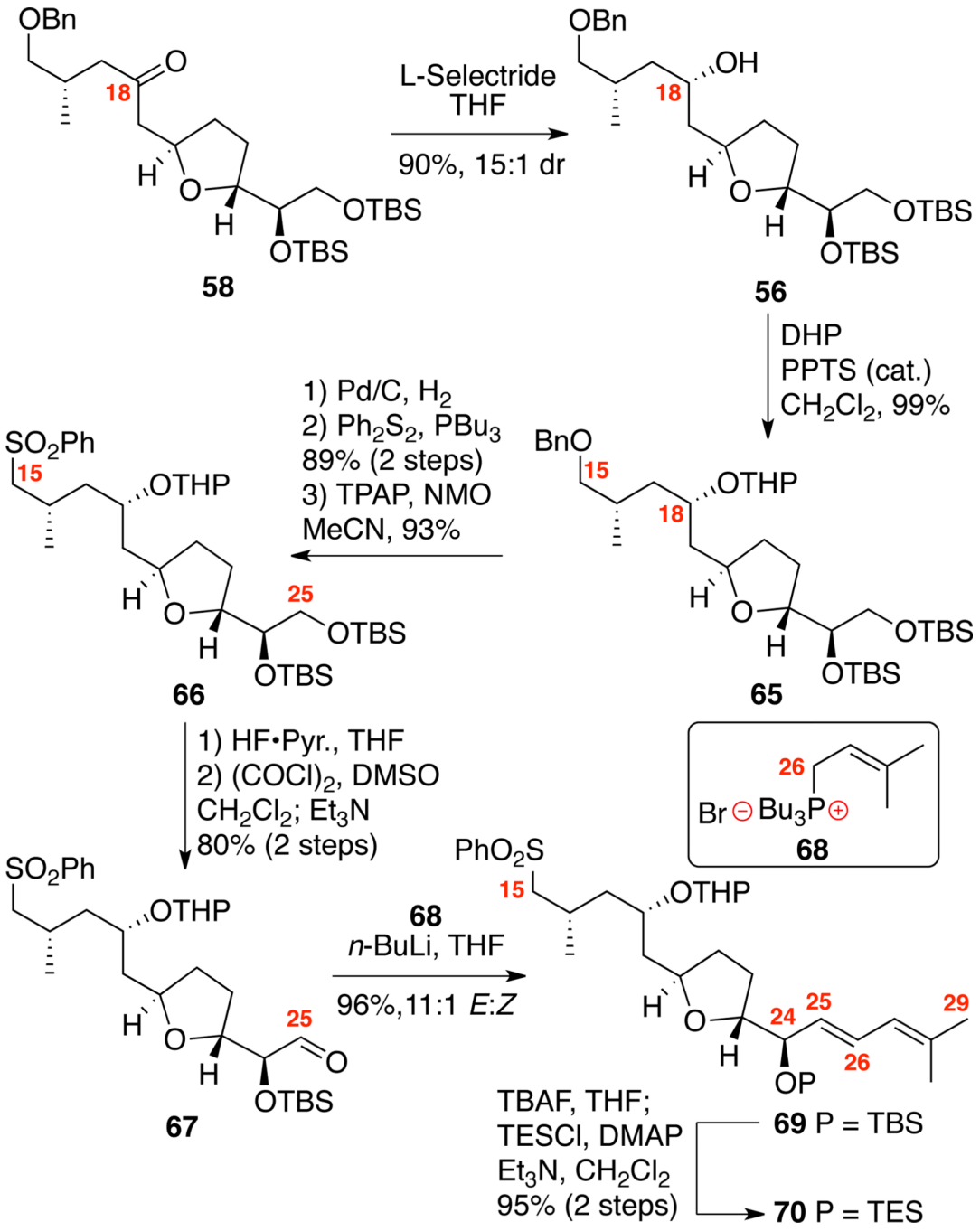
Scheme 8.
Synthesis of the C_1-C_{14} Subunit.



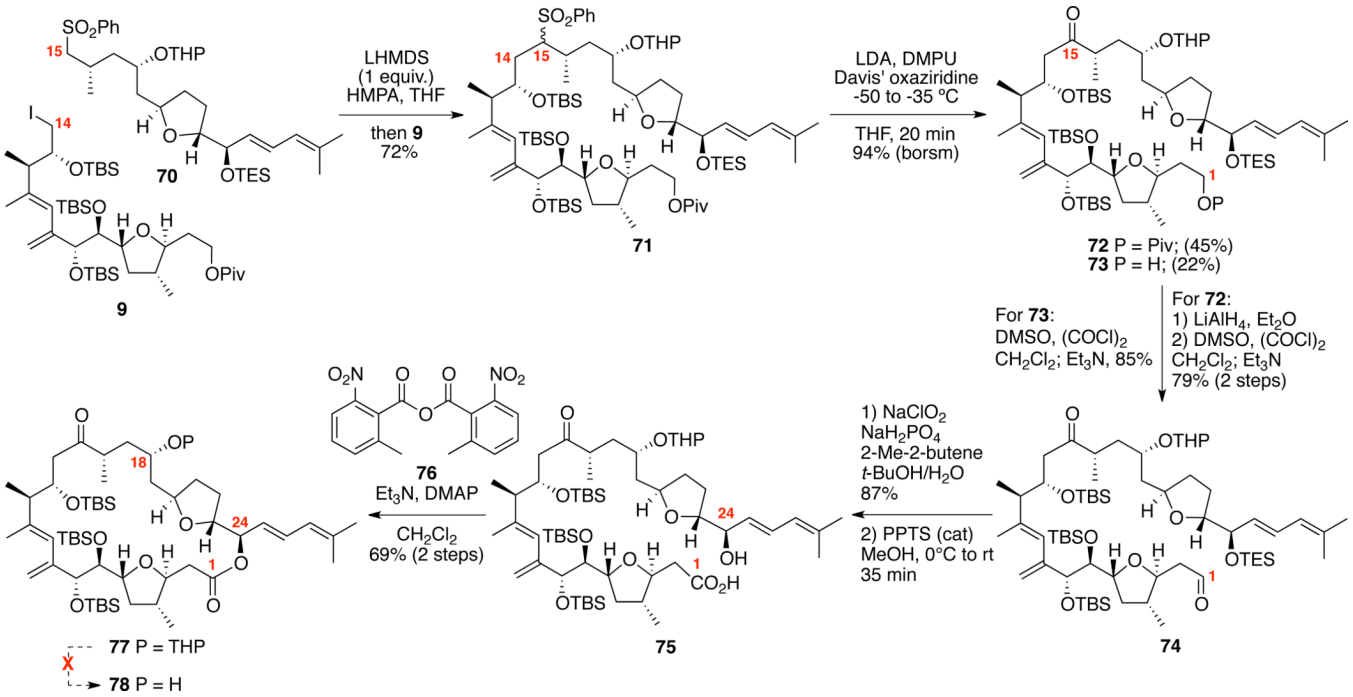
Scheme 9.
Synthesis of the Silyl Enol-ethers.



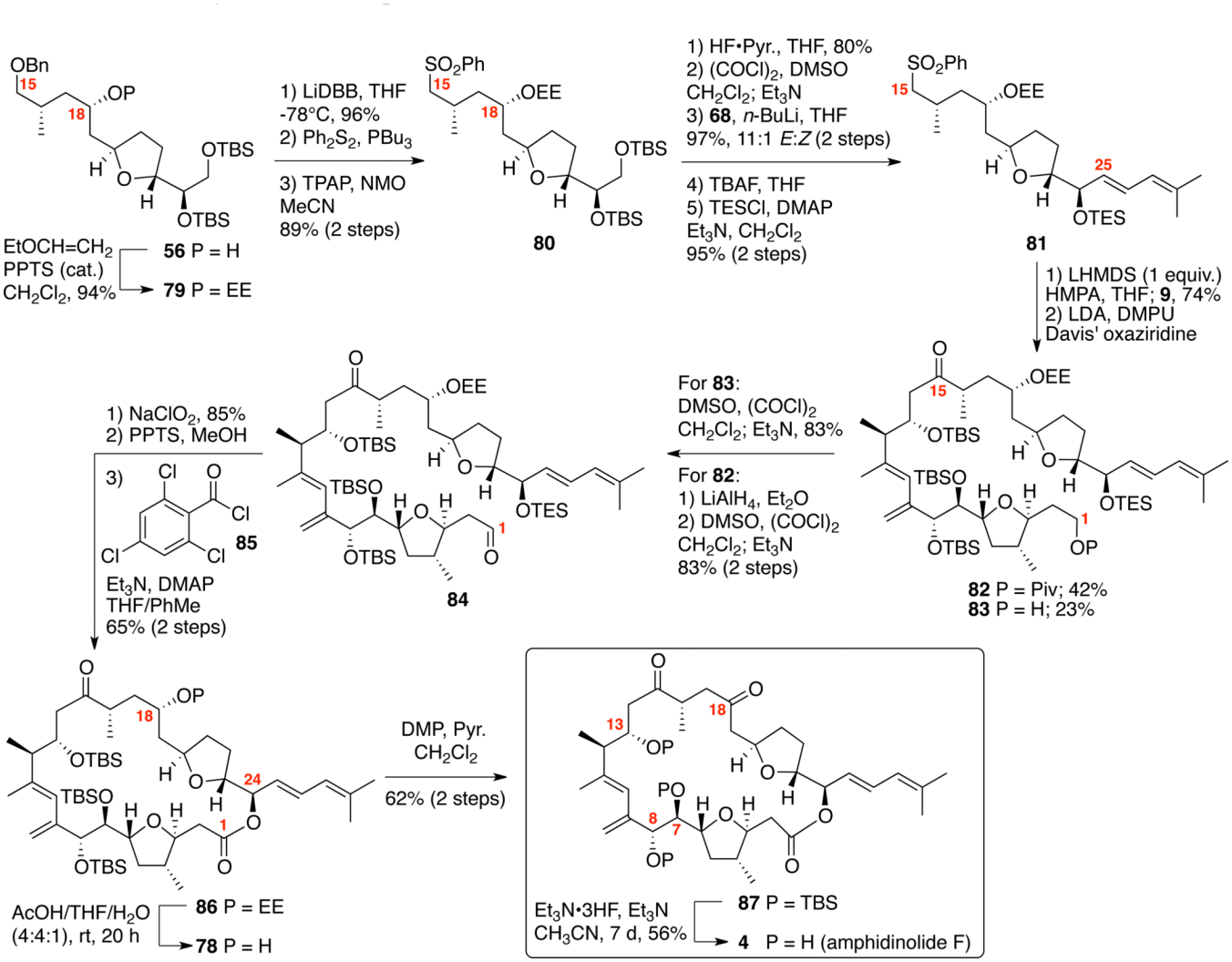
Scheme 10.
Exploration of Silyl Enol-ether Series in Sulfone Alkylation / Oxidative Desulfurization Sequence.



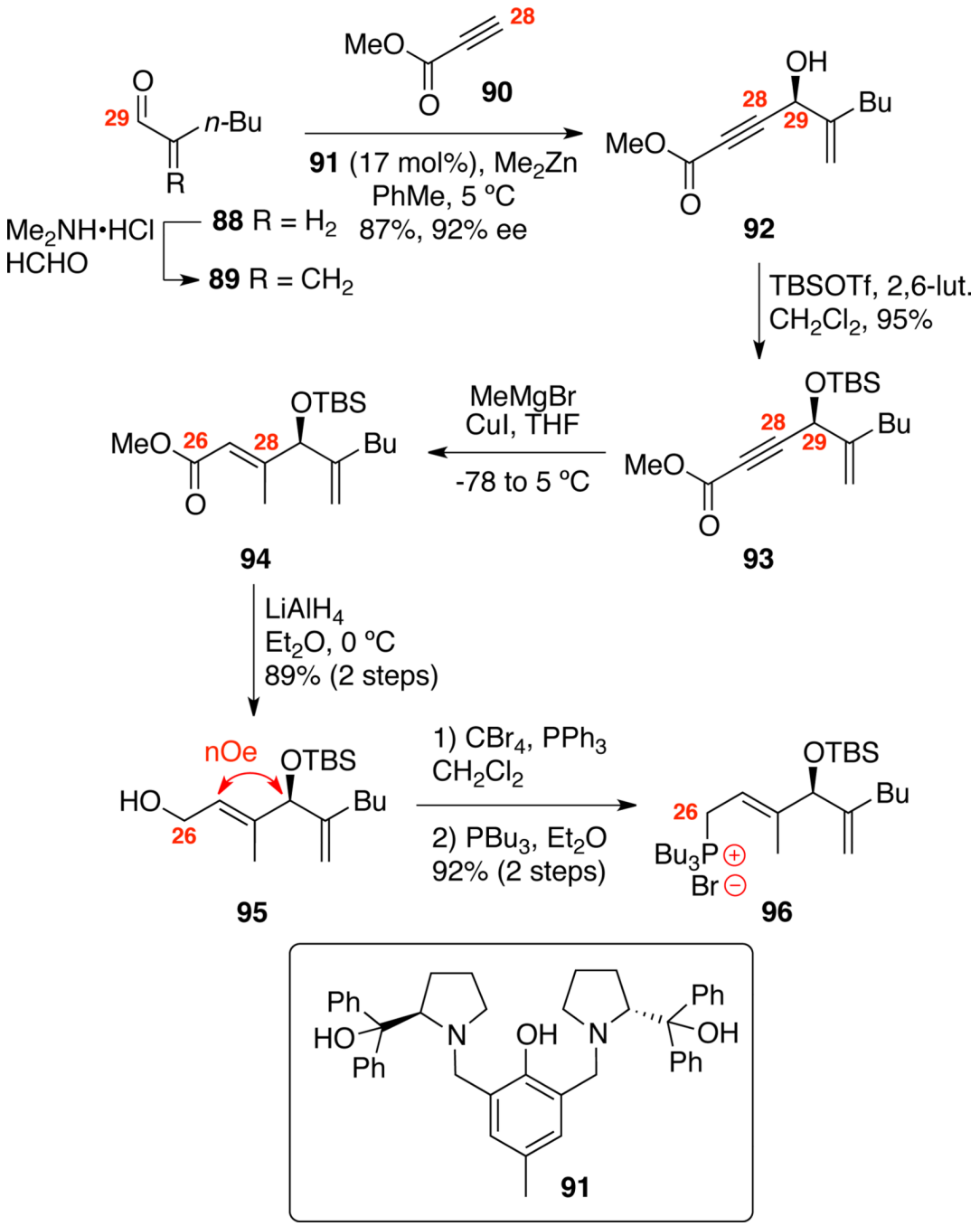
Scheme 11.
Synthesis of the Tetrahydropyranyl Series.



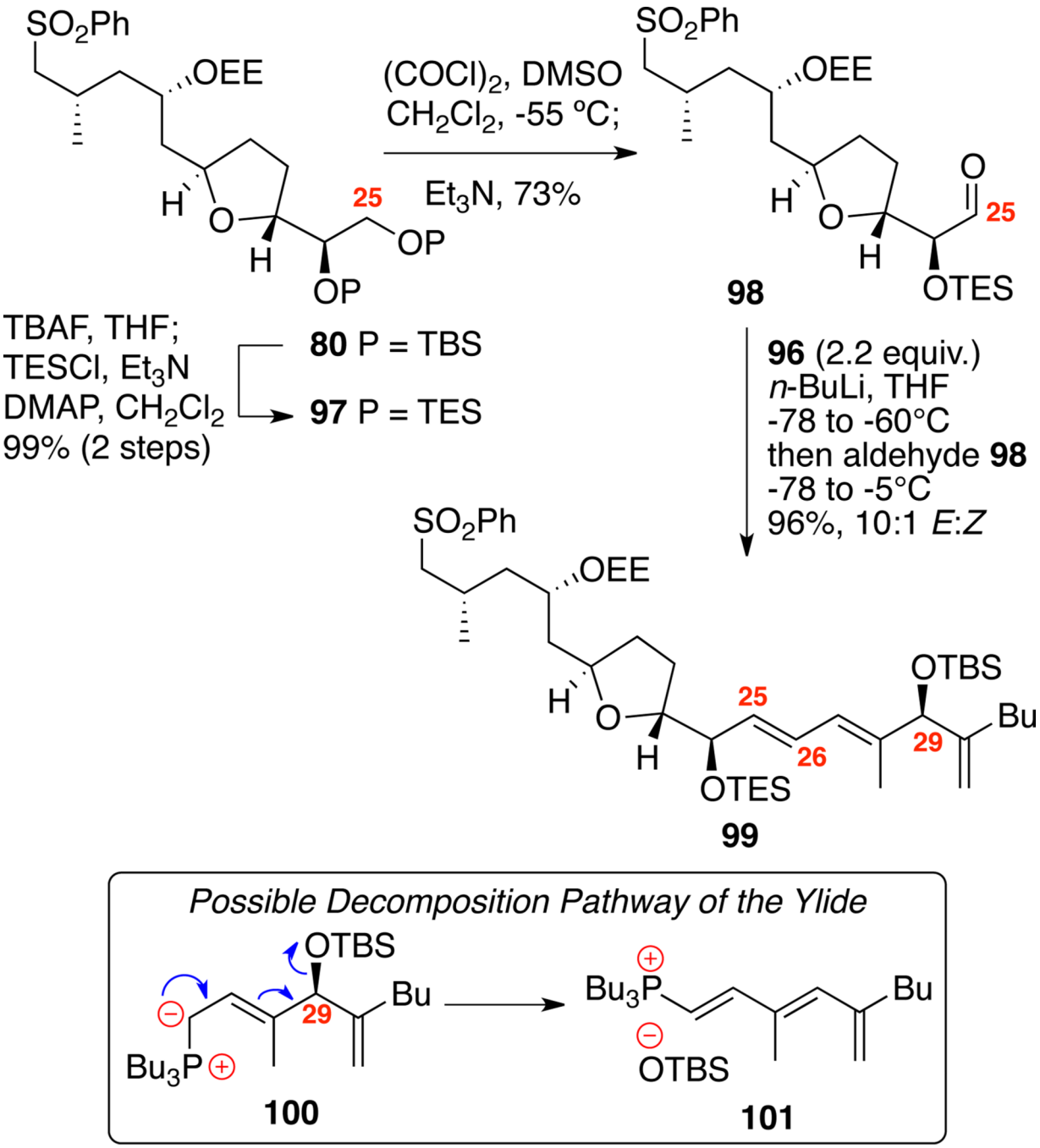
Scheme 12.
Initial Construction of Amphidinolide F Macrocycle.



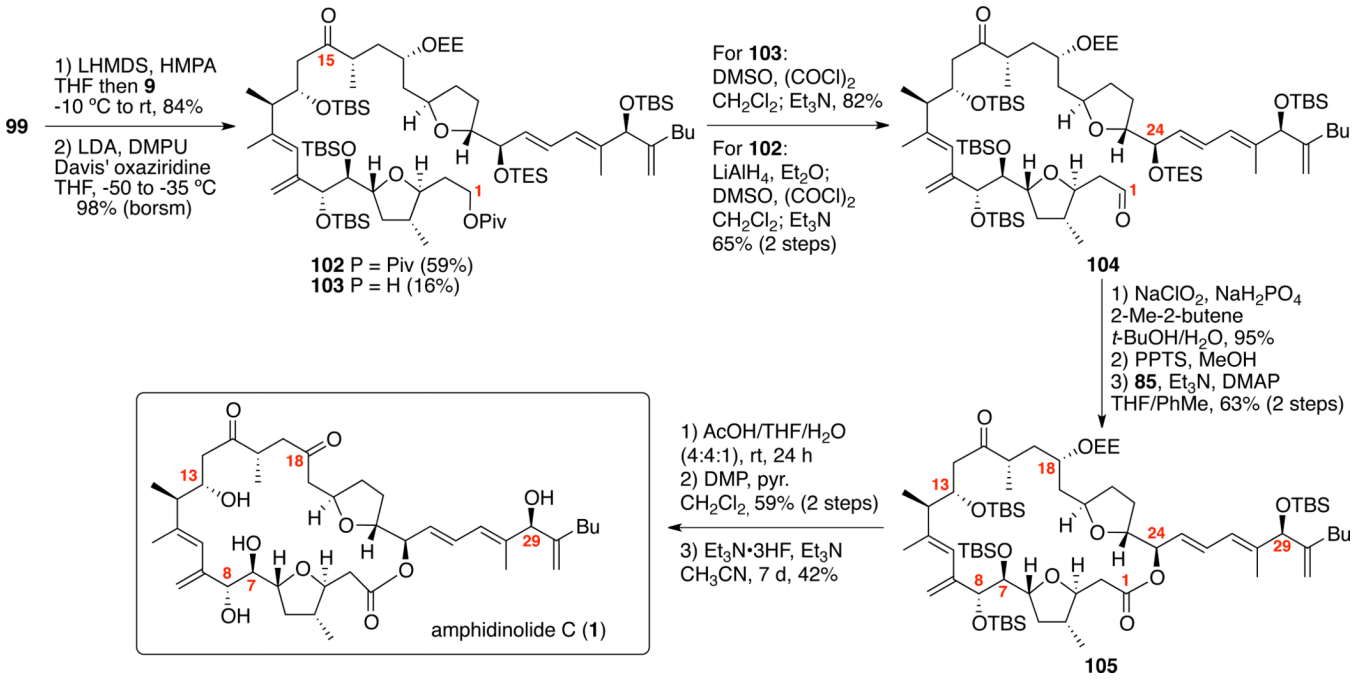
Scheme 13.
Total Synthesis of Amphidinolide F.



Scheme 14.
Synthesis of the Phosphonium Salt.



Scheme 15.
Synthesis of the Sulfone Subunit.



Scheme 16.
Total Synthesis of Amphidinolide C.