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Total Synthesis of Amphidinolide E and Amphidinolide E Stereoisomers

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Abstract

Four amphidinolide E stereoisomers, amphidinolide E (**1**), 2-*epi*-amphidinolide E (**2**), 19-*epi*-amphidinolide E (**3**), and 2-*epi*-19-*epi*-amphidinolide E (**4**), have been synthesized via the judicious union of aldehyde **5**, allylsilanes **7** or **8**, acids **9** or **10**, and vinylstannane **6**. The C19 stereocenters of the C19 epimeric allylsilanes **7** and **8** were introduced via crotylboration reactions early in the synthesis. [3+2]-Annulation reactions of aldehyde **5** with allylsilanes **7** and **8** were employed to set the core tetrahydrofuran units of **1–4**. Finally, the C2 stereocenter was installed by esterification using acid **9**, without incident, or with acid **10**, in which case an unexpected and completely stereoselective inversion of C2 occurs.

Keywords

amphidinolide E stereoisomers; [3+2] annulation reaction; esterification of $Fe(CO)_3$-complexed dienoic acid

1. Introduction

The amphidinolides are a family of biologically active macrolides isolated from the dinoflagellate *Amphidinium* sp.[1] Many of the amphidinolides possess striking cytotoxic properties. Furthermore, this family of natural products exhibits a high degree of structural diversity despite being isolated from a common source. As a consequence, the amphidinolides have attracted considerable interest as targets for synthesis and biological evaluation. Total syntheses of amphidinolides A,[2] J,[3] K,[4] P,[5] T,[6] W,[7] X[8] and Y[9] have been reported.

Amphidinolide E[10] (**1**) is a 19-membered biologically active[1c] macrolactone featuring an embedded 2,5-*cis*-tetrahydrofuran (Figure 1). This structural motif is common within the amphidinolide family. However, the C(1)-C(6) α-chiral, β,γ,δ,ε-dienoate moiety is unique to amphidinolide E. Lee has recently reported the total synthesis of amphidinolide E, [11] while Gurjar[12] and Marshall[13] have published studies toward the synthesis of this interesting natural product.

As part of a program directed towards the synthesis of tetrahydrofuran-containing natural products[14] using a [3+2] annulation strategy, [15,16] we developed and reported a convergent and stereoselective total synthesis of amphidinolide E.[17] In the course of these studies, we encountered an unexpected and highly selective C2 inversion during an esterification reaction

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(**25** + **10** → **39**) that ultimately led to the inadvertent synthesis of 2-*epi*-amphidinolide E (**2**).[18] Initially, we were unaware of this C2 inversion and were faced with the conundrum as to why 2-*epi*-amphidinolide E (**2**), which at the time we thought was structure **1**, did not have spectroscopic properties that matched the data reported in the literature for amphidinolide E (**1**).[10] We describe herein the various structural correlation experiments undertaken to unravel this problem, which ultimately led to the syntheses of amphidinolide E (**1**), 2-*epi*-amphidinolide E (**2**), 19-*epi*-amphidinolide E (**3**), and 2-*epi*-19-*epi*-amphidinolide E (**4**).

2. Results and discussion

2.1 Synthesis of 2-epi-amphidinolide E

We envisioned that amphidinolide E could be obtained by the Stille[19] cross coupling of vinyl iodide **11** with vinylstannane **6** (Figure 1). Macrocycle **11** would be accessed in two steps via esterification of **12** with dienoic acid **13**, followed by ring closing metathesis. Finally, we anticipated that the tetrahydrofuran fragment **12** would arise from the product of the [3+2] annulation of aldehyde **5** and allylsilane **7**.[14a,15]

The synthesis of aldehyde **5** began with the Swern oxidation of alcohol **14**,[20] which is available in five steps from commercially available isopropylidene dimethyl D-tartrate (Scheme 1). Treatment of the aldehyde with vinyl magnesium bromide followed by a Johnson orthoester Claisen rearrangement[21] of the allylic alcohol intermediate afforded methyl ester **15** in 60% overall yield. Reduction of **15** with DIBAL (−78 °C) yielded the targeted aldehyde **5**.

Allylsilane **7** was synthesized starting from homoallylic alcohol **16**,[22] which is available with high diastereoselectivity from the asymmetric (*E*)-crotylboration[23] of L-glyceraldehyde pentylidene ketal[24] (Scheme 2). Protection of **16** as the *p*-methoxybenzyl ether followed by hydroboration-oxidation of the vinyl group provided primary alcohol **17** (90% yield). Oxidation of **17**, by using SO_3·pyridine and DMSO,[25] and subsequent Corey-Fuchs[26] homologation of the aldehyde furnished alkyne **18** (88%). Acidic hydrolysis of the pentylidene ketal protecting group and oxidative cleavage of the resulting diol afforded aldehyde **19**. *anti*-Silylallylboration of **19** was accomplished with 9:1 selectivity (90% yield) by using (*E*)-γ-silylallylboronate (*S*,*S*)-**20**.[27] Protection of the β-hydroxy allylsilane **21** as the triethylsilyl ether provided allylsilane coupling partner **7**. Mosher ester analysis of alcohol **21** confirmed the C17(*S*) hydroxyl stereocenter (Scheme 3).[28] In addition, the C16-C17 relative stereochemistry was confirmed via basic Peterson elimination[29] of **21**, which afforded the *Z* diene **23**.

Initial [3+2] annulations using excess aldehyde **5**, with respect to allylsilane **7**, and substiochiometric amounts of BF_3·Et_2O afforded low yields of product **24** (entry 1, Scheme 4). On the other hand, use of stoichiometric or excess amounts of allylsilane **7** and stoichiometric amounts of Lewis acid led to improved yields of **24** (entries 3–5). The optimum reaction stiochiometry, 2.5 equiv of **7** and 1 equiv of **5**, led to **24** in 48% yield and d.r. >20:1. Use of $SnCl_4$ as the Lewis acid led to trace amounts of **24** and significant decomposition of **7** (entry 2).[30] Excess allylsilane **7** was recovered in excellent yield for all reactions using BF_3·Et_2O. The modest yield of **24** is due to the propensity of **5** to cyclotrimerize under the reaction conditions to give **26**. Slow syringe pump addition of **5** into a −78 °C solution of allylsilane **7** and BF_3·Et_2O failed to improve the yield. In addition, conducting the reaction at temperatures higher than −78 °C resulted in significant Peterson elimination of **7**.

Treatment of [3+2] adduct **24** with solid TBAF·$3H_2O$ in DMF at 90 °C effected smooth sp^3 C–Si bond scission with concomitant removal of the triethylsilyl ether (Scheme 4).[31] Reintroduction of the TES ether, and subsequent oxidative removal of the *p*-methoxybenzyl

group[32] gave alcohol **25**. The *cis*-THF stereochemistry of **24** was confirmed via nOe's shown Figure 2.

Esterification of the C18 hydroxyl group of **25** (or related intermediates **27**, **28**, and **29**) with dienoic acid **13**[33] (or various derivatives of **13**) proved to be extremely challenging (Table 1). Use of excess amounts (10–20 equiv.) of **13** and various coupling reagents invariably failed. The list of unsuccessful esterification reactions included attempts to use the modified Yamaguchi conditions[34] (entry 1), use of mild peptide coupling conditions[35] (entries 2, 3 and 6), use of Otera's transesterification catalyst **30**[36] (entry 5), attempted coupling of the tributyltin ether of **29** with the acylfluoride **32** (entry 7), and generation of the lithium alkoxide of **29** followed by treatment with acylfluoride **32** (entry 8). Kita[37] has developed a two step esterification protocol involving initial formation of a 1-ethoxyvinyl ester derivative of the acid coupling partner using 1-ethoxyacetylene and $\{RuCl_2(p\text{-cymene})\}_2$. This 1-ethoxyvinyl ester derivative is then treated with the alcohol coupling partner and a catalytic amount of a Bronsted acid to achieve the esterification. Lee and co-workers[11] have successfully employed this methodology in a macrolactonization fashion for amphidinolide E. Unfortunately, the Kita conditions proved to be unsuccessful in our intermolecular reaction (entry 9). Whereas in most cases the alcohol was recovered unscathed from these unsuccessful experiments, the acid component was recovered as the fully conjugated, diene migrated species **34**. No more than trace quantities of ester products corresponding to acids **13** or **34** could be isolated from these experiments.

We reasoned that use of a "diene protected" acid **10** might be effective to avoid the problems encountered in attempted esterifications reactions of acid **13**. The synthesis of acid **10** began with the Evans methylation[38] of oxazolidinone **35**[39] to afford product **36** in 79% yield (Scheme 5). Treatment of **36** with $Fe_2(CO)_9$ in benzene at reflux gave a separable 1:1 mixture of **37** and **38**. Hydrolysis of the acyloxazolidinone units of **37** and **38** furnished acids **10** and **9**[40] in 62% and 58% yield, respectively.

Gratifyingly, use of $(CO)_3$Fe-complexed dienoic acid **10** (1.6 equiv) resulted in an efficient esterification with alcohol **25** under the modified Yamaguchi conditions (Scheme 6). *However, the ester product **39** is the unexpected, C2 inverted isomer. Since **39** was formed as a single diastereomer, we had no reason to suspect inversion at C2 and therefore proceeded forward with the synthesis under the assumption that the* 2*S stereochemistry of* **10** *had been preserved after the esterification reaction. It was not until much later (see section 2.4) that we became aware of the C2 inversion in this reaction.*

Oxidative decomplexation of the $(CO)_3$Fe-unit of **39** (96% yield) followed by ring closing metathesis[41,42] (60% yield) afforded the 19-membered macrocycle **40**. Furthermore, an inseparable mixture of products thought to arrive by enyne metathesis was also isolated (15% yield). Use of the more active Grubbs' second generation or Grubbs-Hoveyda catalysts resulted in significant decomposition of the polyene substrate. Diene and triene forming ring closing metathesis macrocyclizations can sometimes be plague with products containing rings smaller than desired.[42a,b] However, none of the smaller macrocycles (16-membered ring and smaller) were observed for the ring closure our polyene substrate. In addition, ruthenium catalyzed ring closing metathesis reactions of substrates containing internal alkynes,[43] unprotected terminal alkynes,[44] and protected terminal alkynes (silylated45 or dicobalt complexed[46]) are rare.

Stannylalumination-protonolysis[47] of the alkyne unit of **40** followed by iododestannylation of the resultant vinylstannane gave vinyl iodide **41**. Acidic hydrolysis of both the triethylsilyl and acetonide protecting groups afforded a 10:1 inseparable mixture of the C18 and C17 lactones. Stille cross coupling of the mixture of lactonic iodides with vinylstannane **6**[12] followed by HPLC purification afforded 2-*epi*-amphidinolide E (**2**), spectroscopic data for which did not

match Kobayashi's spectroscopic data for amphidinolide E (**1**). The most egregious spectroscopic disagreement between **2** and natural amphidinolide E (**1**) was the chemical shift for the H3 proton (6.00 ppm for **2** vs. 5.59 ppm for natural **1**).

2.2 Structural correlations of our intermediates with Kobayashi's amphidinolide E degradation products

In an effort to determine the structural discrepancies between natural amphidinolide E (**1**) and what we believed was our "synthetic amphidinolide E" (**2**), we proceeded to repeat Kobayashi's stereochemical assignments[10b] for **1** using our synthetic intermediates as correlation compounds.

Kobayashi and co-workers transformed natural amphidinolide E (**1**) into two degradation products, the C8-C17 tetrahydrofuran containing fragment **42** and the C1-C7 fragment **43** (Scheme 7).[10] The enantiomer of **42**, namely compound **44**, was independently synthesized by Kobayashi, thereby leading to the assignment of 13*S* and 16*S* stereochemistry in natural amphidinolide E. The 2*R* stereochemistry of natural amphidinolide E was assigned by analogy to data for a small set of structures containing primary Mosher esters with adjacent methyl-branched stereocenters.[48] This precedent indicated that the difference in chemical shifts for the diastereotopic C1 methylene protons were typically smaller for (*S*)-MTPA esters when the adjacent methyl-branched stereocenter has *R* stereochemistry. We were concerned about the reliability of this method for absolute stereochemical assignment, given the small number of literature examples, and therefore resolved to make an unequivocal stereochemical assignment for C2 by independently synthesizing the C1-C7 fragment **43** from a chiral pool starting material, aldehyde **45**[49] (Scheme 8). Olefination of aldehyde **45** afforded product **46**.[50] Hydrogenation of **46** in EtOAc-MeOH over Pd/C occurred with concomitant hydrolysis of the primary TBS ether. Oxidative removal of the PMB ether of **47** followed by Mosher ester formation yielded the C1-C7 fragment **43**. The ^{1}H NMR data for our synthetic **43** matched Kobayashi's data exactly. Therefore C2 of **43**, and hence also of amphidinolide E, is *R*.

Kobayashi and co-workers treated natural amphidinolide E with 2,2-dimethoxypropane and *p*-toluenesulfonic acid to generate the C7-C8 acetonide derivative **49** (Scheme 9).[10] The magnitude of the H7-H8 coupling constant and the indicated NOESY correlation peaks of **49** formed the basis for assignment of threo C7-C8 relative stereochemistry. The C7 and C8 absolute stereochemistry was assigned by application of the exciton chirality method[51] for the 7,8-*bis*-cinnamoyl ester derivative **50**. The CD spectrum of **50** showed a negative first Cotton effect (λ_{ext} 324 nm, $\Delta\varepsilon$ -14.3) and positive second Cotton effect (λ_{ext} 289 nm, $\Delta\varepsilon$ +18.9), indicating 7*R* and 8*R* absolute stereochemistry.[52]

Kobayashi's NMR analysis of the 7,8,17-*tris*-MTPA ester derivative **51** confirmed the 7*R* and 8*R* assignments and determined the 17*R* stereocenter of natural amphidinolide E (Scheme 10a).[10] Deprotection of our ring closing metathesis product **40**, followed by Mosher ester formation afforded the synthetic correlation Mosher triester **52** (Scheme 10b). Mosher triester **52** lacks the complete side chain of Kobayashi's intermediate **51**. Therefore, the magnitudes of the chemical shift differences for the (*S*) versus (*R*)-MTPA ester derivatives were not expected to be identical. However, if the stereocenters in **51** and **52** were the same, we expected the directionalities of the chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) to correlate. This held true at every position except for C17 and C3. We thought this discrepancy was an indication that we had incorrectly assigned the C16 stereochemistry of **52**, and ultimately **40** and **25**, as 16*S* and that perhaps the correct stereochemistry is 16*R*. Therefore, our intermediate **25** was transformed into Kobayashi's C8-C17 fragment **42** in eight standard steps (Scheme 11). The ^{1}H NMR data for our synthetic **42** matched Kobayashi's data, thereby confirming that our original 16*S* stereochemical assignment was correct.

Kobayashi and co-workers assigned the C18 and C19 stereocenters by synthesizing the *bis*-acetonide intermediate **55** from natural amphidinolide E in three steps (Scheme 12).[10] The NOESY correlation peaks of **55** established a threo C17-C18 relationship. In addition, the H18-H19 and H18-C28 coupling constants of **1** supported a erythro C18-C19 relationship. The red NOESY peak in **55** was also used to support the C18-C19 relative assignment. We felt that the NOESY peaks shown for **55** were not unique for the 19*R* (erythro C18-C19) stereochemical assignment of **55**. It is possible that the C19-epimer of **55**, compound **56** (19*S* instead of 19*R*), could exhibit the same NOESY peaks and coupling constant data. Therefore, we considered the possibility that C19 might have been originally misassigned.

Based upon the correlation experiments described above, we thought that we had confirmed the C7, C8, C13, C16, C17 ***and the C2*** stereochemistry of both natural amphidinolide E as well as our synthetic intermediates. In addition, we felt that Kobayashi's C18 stereochemical assignment was irrefutable. Therefore, we concluded at this stage that the structure of natural amphidinolide E most likely was **57**, with 19*S* instead of 19*R* stereochemistry (Figure 3).

2.3 Synthesis of 2-epi-19-epi-amphidinolide E

The 19*S* stereochemistry in the possible alternative structure of amphidinolide E (**57**) was incorporated into our synthetic route by using *Z*-(*S*,*S*)-crotylboronate **59**[23] for the asymmetric crotylboration of L-glyceraldehyde pentylidene ketal **58.**[24] This experiment provided homoallylic alcohol **60** in good diastereoselectivity (Scheme 13). Elaboration of **60** into allylsilane **8** was accomplished using steps analogous to our original route shown previously in Scheme 2.

The [3+2] annulation reaction between allylsilane **8** (3 equiv) and aldehyde **5** provide **65** with >20:1 selectivity in 61% yield (Scheme 14). The excess **8** can be recovered with excellent efficiency (92%). The [3+2] adduct **65** was transformed into alcohol **67** using the same sequence as described for the synthesis of **25** (Scheme 4).

The C16-C17 relative stereochemistry of **8** was confirmed via basic Peterson elimination to afford the *Z* diene **68** (Scheme 15). Assessment of the C17 absolute stereochemistry was attempted by direct esterification of the hydroxyl group in **8** with (*R*) and (*S*)-MTPA-Cl. However, the hydroxyl group of **8** is quite hindered and no reaction was observed. Therefore, confirmation of the C17 absolute stereochemistry was accomplished by the Mosher ester analysis of alcohol **66**.

Esterification of alcohol **67** with acid **10** afforded **70** as single diastereomer with complete inversion of the C2 stereochemistry (Scheme 16). *Again, we had no reason to suspect inversion at C2 due to the high diastereoselectivity and the very clean "spot to spot" nature of the reaction*. Elaboration of **70** into 2-*epi*-19-*epi*-amphidinolide E (**4**) was accomplished using the same chemistry as described for the synthesis of 2-*epi*-amphidinolide E (**2**) (Scheme 6). However, it should be mentioned that a small amount of the presumed enyne side products was once again observed during the ring closing metathesis reaction (10%). In addition, the acidic deprotection of **71** afforded a 2:1 inseparable mixture of the regioisomeric C18 (desired) and C17 lactones. Stille coupling of this mixture with vinylstannane **6** followed by HPLC separation of the isomers afforded pure **4**. To our dismay, spectroscopic properties of 2-*epi*-19-*epi*-amphidinolide E (**4**), which at this stage we thought was structure **57**, once again did not match Kobayashi's data for natural amphidinolide E.

2.4 Discovery of the C2 inversion problem and synthesis of amphidinolide E (1) and 19-epi-amphidinolide E (3)

After synthesizing what we thought were structures **1** and **57** (i.e. syntheses of 2-*epi*-amphidinolide E (**2**) and 2-*epi*-19-*epi*-amphidinolide E (**4**)) only to arrive at material that did not match Kobayashi's natural amphidinolide E, we decided to revisit the original 19*R* series of compounds in order to obtain more insight into the true structure of amphidinolide E (reaction pathway B, Scheme 17). Critically, we had consumed all of our supply of acid diastereomer **10** and decided to use the large supply of diastereomer **9** that had accumulated in our laboratory (reaction pathway A, Scheme 17). Use of either acid diastereomer **9** or **10** should lead to polyene **72** after oxidative decomplexation of the $(CO)_3Fe$ unit if C2 inversion were not occurring. To our surprise, we discovered that esterification-decomplexation reactions using **9** and **10** did not converge to one compound. Instead, they each separately yielded different polyenes **72** and **73** as single diastereomers. Before this discovery, we had always thought that the esterification-decomplexation sequence involving **10** was yielding polyene **72**. Instead, it became absolutely clear based on the following examples that use of acid **10** in this sequence afforded polyene **73**, proceeding through **39**, with clean inversion at C2.

The discovery of separate, divergent reaction pathways for acids **9** and **10** prompted the evaluation of the C2 stereocenter in intermediates both prior to and after the esterification reaction (Table 2). In addition, the starting material used in the synthesis of both **9** and **10**, oxazolidinone **36**, was also evaluated. Table 2 summarizes these correlation experiments. Compounds **36**, **9**, **10**, **76** and **39** were transformed into diene **75**. The optical rotations of **75** from each reduction sequence were then compared with material independently synthesized from aldehyde **45**,[49] using the method of Keck.[53] The 2*R* stereochemistry of **36** was verified prior to complexation of the $(CO)_3Fe$ unit and hydrolysis of the acyloxazolidinone (entry 1, Table 2). The 2*S* stereochemistry of acids **9** and **10** was also verified prior to being subjected to the esterification reactions (entries 2 & 3, Table 2). Furthermore, the C2 stereochemistry of ester **76**, the product of esterification of **25** with acid **9**, was confirmed as 2*S* (entry 4, Table 2). On the other hand, the data in entry 5 indisputably affirms that inversion at C2 occurs when acid **10** is used in the esterification reaction of **25**.

We were pleased to find that subjection of polyene **72** to the same sequence of reactions used to synthesized 2-*epi*-amphidinolide E (**2**) and 2-*epi*-19-*epi*-amphidinolide E (**4**) afforded synthetic amphidinolide E (**1**), which had spectroscopic properties that matched natural amphidinolide E (Scheme 18). Interestingly, it should be noted that, unlike the 2-*epi*-series, the acidic deprotection of **77** only afforded the desired C18 lactone and none of the undesired C17 regioisomeric lactone. As observed before, a mixture of products thought to arrive by enyne metatesis was also isolated in 10 % yield.

Furthermore, we also synthesized the final C2 and C19 stereochemical permutation, 19-*epi*-amphinolide E (**3**) (Scheme 19). Only the C18 lactone was observed in the deprotection of **79**. Furthermore, only a 5% yield of presumbed enyne products was observed during the RING CLOSING METATHESIS reaction. During the course of the synthesis of **3**, we treated **78** with K_2CO_3 (0.9 equiv) in methanol at 50 °C for 3 h and obtained a 2.6:1 mixture of C2 diastereomers favoring **78**. This experiment establishes that the epimerizations observed in the esterifications of **25** (Scheme 6) and **67** (Scheme 16) with the diastereomeric $Fe(CO)_3$-complexed dienoic acid (*2S*,*3S*)-**10** are contrathermodynamic, and therefore also kinetically controlled.[18]

We hypothesize that ketene intermediates may be involved in the esterification reactions with $(CO)_3Fe$-complexed acids **9** and **10** (Scheme 20). Ketene intermediates have previously been implicated by Fürstner and co-workers in studies of the Yamaguchi macrolactonization

directed towards iejimalide B.[54] Activation of acid **10** followed by elimination could afford ketene intermediate **81**. Addition of the alcohol coupling partner (HO-R) to **81** and subsequent reformation of the C2 stereocenter via diastereoselective protonation of enol **82** anti to the $(CO)_3$Fe unit would yield the observed C2 invert product **80**. Alternatively, DMAP could add to the ketene intermediate **81**.[55] Diastereoselective protonation of enolate **83** followed by alkoxide addtion to acyl pyridinium **84** could also afford product **80**.

Matching spectroscopic details for natural and synthetic amphidinolide E are summarized in Table 3, confirming the validity of the originally assigned structure. Characteristic ^{1}H NMR data for all four amphidinolide stereoisomers (**1**–**4**) are presented in Table 4. It is noteworthy, that the H3 resonance is substantially shifted up field relative to amphidinolide E for both C2 epimers (**2** and **4**). Furthermore, the C30-Me resonance is also shifted up field for **2** and **4**. On the other hand, the C29-Me is shifted downfield in the 19-*epi*-series (**3** and **4**). Only the data for synthetic **1** matches that of the natural product.

3. Conclusion

In conclusion, we have synthesized four stereoisomers of amphidinolide E, namely amphidinolide E (**1**), 2-*epi*-amphidinolide E (**2**), 19-*epi*-amphidinolide E (**3**), and 2-*epi*-19-*epi*-amphidinolide E (**4**). This constitutes a rigorous verification of the stereochemistry of amphidinolide E.[56] In the course of the studies toward **1**, we discovered an unexpected and highly selective C2 inversion in the esterification reaction of $(CO)_3$Fe-complexed dienoic acid **10**. Insight into the possible mechanism of this epimerization, the context of which depends on the steric environment of the alcohol, has been published elsewhere.[18] Results of the biological evaluation of **2**, **3**, and **4** will be reported in due course.

4. Experimental

General Experimental Details

All reaction solvents were purified before use. Tetrahydrofuran, dichloromethane, diethyl ether, and toluene were purified by passing through a solvent column composed of activated A-1 alumina. Unless indicated otherwise, all reactions were conducted under an atmosphere of argon using flame-dried or oven-dried (170 °C) glassware. Four Å molecular sieves were activated under high vacuum with heat (180 °C) for 12 h and re-activated by thorough flame-drying immediately prior to use.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on commercial instruments at 400 or 500 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 and 125 MHz, respectively. The proton signal for residual non-deuterated solvent (δ 7.26 for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.2 resonance of $CHCl_3$. Coupling constants are reported in Hz. Infrared (IR) spectra were recorded as films on a FTIR instrument. Opitcal rotations were measured on a polarimeter using a quartz cell with 1 mL capacity and a 10 cm path length. Mass spectra were recorded on a commercial spectrometer.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with Hanessian solution (ceric sulfate and ammonium molybdate in aqueous sulfuric acid). Column chromatography was generally performed using Kieselgel 60 (230–400 mesh) silica gel, typically using a 50–100:1 weight ratio of silica gel to crude product.

HPLC purifications were performed by using a HPLC system composed of two Varian Prostar pumps (model 210) connected to normal phase columns. Samples were loaded into the system

with a 2 mL Rheodyne 7125 injector and were detected using a Varian Prostar UV and a Varian RI detector.

(*E*)-5-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-pent-4-enoic acid methyl ester (15)

To a −78 °C solution of $(COCl)_2$ (3.45 mL, 39.4 mmol) in CH_2Cl_2 (80 mL) was added DMSO (3.50 mL, 49.2 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred at −78 °C for 15 min, then alcohol **14**[20] (3.12 g, 19.7 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 20 min at −78 °C followed by the addition of triethylamine (16.4 mL, 118 mmol). The mixture was allowed to warm to 0 °C. After 30 min, the reaction was diluted with Et_2O (300 mL), upon which a white precipitate forms (triethylamine hydrochloride). The slurry was filtered through a 1 inch pad of Celite and concentrated to afford the aldehyde, a yellow oil, which was immediately used in the next reaction.

To a 0 °C solution of the crude aldehyde in THF (60 mL) was added vinylmagnesium bromide (60 mL of a 1.0M THF solution, 60 mmol). The reaction was stirred for 2.5 h, and then quenched with saturated aqueous $NaHCO_3$ (50 mL) and extract with Et_2O (20 mL × 3). The organic phase was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a mixture of diastereomeric allylic alcohols as a yellow oil. This oil was used immediately in the next reaction.

To the mixture of diastereomeric allylic alcohols, from the preceding step, in toluene (66 mL) was added trimethyl orthoacetate (12.5 mL, 98.5 mmol) and propionoic acid (0.3 mL, 3.94 mmol). The reaction was fitted with a condenser and placed in a 110 °C oil bath for 18 h. The solution was then quenched with 3 mL of triethylamine and concentrated. The crude product was purified by flash column chromatography to yield methyl ester **15** (2.83 g, 60% over 3 steps) as a colorless oil: $[\alpha]^{25}_D = -132°$ (*c* 0.99, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.74-5.83 (m, 2H), 5.48 (dd, *J* = 6.4, 15.2 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.04 (app q, *J* = 6.8 Hz, 2H), 3.67 (s, 3H), 2.36-2.44 (m, 4H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172. 8, 134.0, 133.7, 126.9, 118.3, 108.7, 82.0, 81.6, 51.3, 33.1, 27.3, 26.8, 26.7; IR (neat) 2987, 2874, 1740, 1437, 1371 cm^{-1}; HRMS (ES+) *m/z* for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ calcd 263.1259, found 263.1255.

(*E*)-5-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-pent-4-enal (5)

To a −78 °C solution of methyl ester **15** (2.25 g, 9.36 mmol) in toluene (31 mL) was added DIBAL (9.36 mL of a 1.0M hexane solution, 9.36 mmol) dropwise such that the internal temperature was below −70 °C. After being stirred for 30 min, the reaction was quenched with saturated aqueous sodium potassium tartrate (Rochelle's salt) (40 mL) and diluted with Et_2O (20 mL). The mixure was stirred at room temperature for 3 h and extracted with Et_2O (20 mL × 3). The organic phase was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography to afford aldehyde **5** (1.59 g, 81%) as a colorless oil: $[\alpha]^{25}_D = -28.7°$ (*c* 1.41, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.73 (bs, 1H), 5.70-5.85 (m, 2H), 5.49 (bdd, *J* = 6.0, 15.6 Hz, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.00-4.10 (m, 2H), 2.52-2.60 (m, 2H), 2.35-2.45 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 201.3, 134.1, 133.8, 127.2, 118.8, 109.0, 82.2, 81.8, 42.8, 27.0, 27.0, 24.7; IR (neat) 3085, 2987, 2875, 1726, 1379, 1371, 1239 cm^{-1}; HRMS (ES+) *m/z* for $C_{13}H_{20}O_3Na$ $[M+Na]^+$ calcd 233.1154, found 233.1245.

(3*R*,4*R*)-4-((*S*)-2,2-Diethyl-[1,3]dioxolan-4-yl)-4-(4-methoxy-benzyloxy)-3-methyl-butan-1-ol (17)

To a 0 °C slurry of NaH (1.69 g, 70.6 mmol) and Bu_4NI (1.7 g, 4.7 mmol) in THF (157 mL) was added homoallylic alcohol **16**[22] (10.1 g, 47.0 mmol) followed by *p*-methoxybenzyl chloride (6.38 mL, 47. 0 mmol). The reaction was fitted with a condenser and refluxed for 16

h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and water (50 mL) and extracted with EtOAc (25 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afforded the *p*-methoxybenzyl ether (15.15 g, 96%) as a colorless oil: $[\alpha]^{25}_D = -41°$ (*c* 1.53, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.86 (ddd, *J* = 8.0, 10.4, 17.2 Hz, 1H), 5.04 (app t, *J* = 17.6 Hz, 2H), 4.60 (AB, *J* = 10.8 Hz, 1H), 4.55 (AB, *J* = 11.2 Hz, 2H), 4.05-4.10 (m, 1H), 4.00 (dd, *J* = 6.0, 7.6 Hz, 1H), 3.81 (s, 3H), 3.77 (d, *J* = 7.6 Hz, 1H), 3.52 (dd, *J* = 3.6, 6.0 Hz, 1H), 2.50-2.54 (m, 1H), 1.57-1.70 (m, 4H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.89 (dt, *J* = 9.6, 7.6 Hz, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.1, 140.1, 130.1, 129.3, 115.0, 113.7, 112.1, 83.1, 77.3, 74.0, 66.9, 55.2, 40.8, 29.7, 29.0, 17.0, 8.2, 8.1; IR (neat) 3073, 2972, 1613, 1514, 1249 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{30}O_4Na$ $[M+Na]^+$ calcd 357.2042, found 357.2044.

To a solution of the *p*-methoxybenzyl ether (15.1 g, 45.3 mmol) in THF (181 mL) was added 9-BBN (272 mL of a 0.5 M THF solution, 136 mmol). The reaction was fitted with a condenser, refluxed for 3 h, cooled to 0 °C and quenched with water (25 mL). The mixure was then treated with 2N NaOH aq. (227 mL) followed by 30% (w/w) H_2O_2 (46.3 mL) and the biphasic mixture was stirred at room temperature for 17 h. The aqueous phase was extracted with EtOAc (50 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford **17** (15.1 g, 94%) as a colorless oil: $[\alpha]^{25}_D = -27°$ (*c* 0.63, $CHCl_3$); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.56 (s, 2H), 4.16 (app q, *J* = 6.5 Hz, 1H), 4.07 (dd, *J* = 6.0, 8.0 Hz, 1H), 3.80 (s, 3H), 3.75 (app t, *J* = 8.0 Hz, 1H), 3.70-3.76 (m, 1H), 3.60-3.64 (m, 1H), 3.46 (dd, *J* = 4.5, 6.0 Hz, 1H), 2.02-2.07 (m, 1H), 1.95 (dd, *J* = 4.5, 6.0 Hz, 1H), 1.73-1.79 (m, 1H), 1.58-1.67 (m, 4H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.89 (dt, *J* = 7.0, 5.5 Hz, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 159.2, 130.3, 129.3, 113.7, 112.6, 83.3, 77.3, 76.3, 67.7, 60.5, 55.2, 34.9, 32.1, 29.7, 29.0, 16.3, 8.2; IR (neat) 3436, 2971, 2881, 1613, 1514, 1249 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{32}O_5Na$ $[M+Na]^+$ calcd 375.2147, found 375.2141.

(*S*)-2,2-Diethyl-4-[(1*R*,2*R*)-1-(4-methoxy-benzyloxy)-2-methyl-pent-4-ynyl]-[1,3]dioxolane (18)

To a 0 °C solution of alcohol **17** (15.0 g, 42.6 mmol) in CH_2Cl_2 (142 mL) was added DMSO (9.1 mL, 128 mmol), *i*-Pr_2NEt (22.2 mL, 128 mmol) and SO_3·Pyr (20.3 g, 128 mmol). The reaction was stirred at 0 °C for 30 min, then quenched with sat. aq. $Na_2S_2O_3$ (100 mL) and extracted with CH_2Cl_2 (30 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford the aldehyde (13.39 g, 89%) as a colorless oil: $[\alpha]^{25}_D = -30°$ (*c* 2.2, $CHCl_3$); ^{1}H NMR (500MHz, $CDCl_3$) δ 9.73 (app t, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.56 (AB, *J* = 11.0 Hz, 1H), 4.53 (AB, *J* = 11.0 Hz, 1H), 4.12 (dd, *J* = 6.5, 13.0 Hz, 1H), 4.06 (dd, *J* = 6.5, 8.0 Hz, 1H), 3.80 (s, 3H), 3.73 (t, *J* = 8.0 Hz, 1H), 3.40 (dd, *J* = 4.5, 6.0 Hz, 1H), 2.65 (ddd, *J* = 2.0, 6.0, 7.5 Hz, 1H), 2.43-2.48 (m, 1H), 2.37 (ddd, *J* = 2.0, 7.5, 9.5 Hz, 1H), 1.57-1.67 (m, 4H), 1.06 (d, *J* = 7.5, Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 202.2, 159.2, 130.2, 129.4, 113.7, 113.0, 82.2, 76.1, 73.3, 67.6, 55.2, 47.1, 30.3, 29.7, 28.9, 16.5, 8.2, 8.2; IR (neat) 2971, 2934, 2724, 2721, 1724, 1514, 1249 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{30}O_5Na$ $[M+Na]^+$ calcd 373.1991, found 373.1984.

To a 0 °C solution of PPh_3 (24.9 g, 94.87 mmol) in CH_2Cl_2 (182 mL) was added CBr_4 (15.7 g, 47.4 mmol). The reaction was warmed to room temperature for 30 min and then cooled back to 0 °C. To this mixture was added the aldehyde from the preceding step (12.8 g, 36.5 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 30 min and then diluted with hexane (400 mL), upon which a white precipitate formed (Ph_3P=O). The slurry was filtered through Celite and concentrated. The residue was dissolve in hexane (300 mL) to precipitate more Ph_3P=O. The

slurry was filtered through Celite and again concentrated. The residual oil was dissolved in THF (100 mL), cooled to −78 °C and treated with n-BuLi (32.4 mL of 2.29M hexane solution, 74.3 mmol). The reaction was stirred for 1h and then quenched with sat. aq. NH_4Cl (100 mL) and extracted with EtOAc (50 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography afforded **18** (11.0 g, 98%) as a colorless oil: $[\alpha]^{25}_D = -7.6°$ (*c* 0.89, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.62 (AB, *J* = 10.8 Hz, 1H), 4.54 (AB, *J* = 11.2 Hz, 1H), 4.17 (dt, *J* = 6.0, 8.0 Hz, 1H), 4.03 (dd, *J* = 6.0, 8.0 Hz, 1H), 3.80 (s, 3H), 3.77 (t, *J* = 8.0 Hz, 1H), 3.57 (t, *J* = 6.0 Hz, 1H), 2.27-2.39 (m, 2H), 1.98 (app t, *J* = 3.2 Hz, 1H), 1.91-1.98 (m, 1H), 1.56-1.71 (m, 4H), 1.10 (d, *J* = 7.2 Hz, 3H), 0.90 (app q, *J* = 7.6 Hz, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.2, 130.5, 129.4, 113.7, 112.8, 83.2, 81.2, 76.5, 73.7, 69.4, 67.0, 55.2, 34.9, 29.7, 29.0, 22.1, 15.7, 8.2, 8.1; IR (neat) 3295, 2971, 1613, 1514 cm^{-1}; HRMS (ES+) *m/z* for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ calcd 369.2042, found 369.2037.

(2*R*,3*R*)-2-(4-Methoxy-benzyloxy)-3-methyl-hex-5-ynal (19)

To alkyne **18** (4.84 g, 14.0 mmol) was added a 4:1 mixture of AcOH and water (47 mL). The reaction mixture was heated to 40 °C for 6 h and then was diluted with 50 mL of EtOAc. Solid $NaHCO_3$ (20 g) was slowly added portionwise and then the mixture was extracted with EtOAc (25 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford the diol (3.39 g, 87%) as a colorless oil: $[\alpha]^{25}_D = +13.6°$ (*c* 0.59, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.64 (AB, *J* = 11.2 Hz, 1H), 4.61 (AB, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.69-3.84 (m, 3H), 3.58 (dd, *J* = 4.4, 7.2 Hz, 1H), 2.33-2.46 (m, 3H), 2.18 (dd, *J* = 4.0, 8.0 Hz, 1H), 2.03 (t, *J* = 2.4 Hz, 1H), 1.96-2.02 (m, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.4, 130.3, 129.6, 113.9, 83.8, 83.0, 74.8, 71.5, 69.9, 63.3, 55.3, 34.4, 21.9, 16.3; IR (neat) 3413, 3306, 2936, 1612, 1515, 1249 cm^{-1}; HRMS (ES+) *m/z* for $C_{16}H_{22}O_4Na$ $[M+Na]^+$ calcd 301.1416, found 301.1416.

To a 0 °C solution of the diol (3.39 g, 12.2 mmol) in THF (20 mL) and pH 7 buffer (20 mL) was added $NaIO_4$ (3.13 g, 14.6 mmol). The reaction was stirred for 4 h, quenched with sat. aq. $Na_2S_2O_3$ (25 mL) and extracted with EtOAc (25 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford pure **19** (2.76 g, 92%) as a colorless oil: $[\alpha]^{25}_D = +80°$ (*c* 2.26, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 9.65 (app d, *J* = 3.0 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.60 (dd, *J* = 3.0, 10.0 Hz, 1H), 2.34-2.36 (m, 2H), 2.11-2.17 (m, 1H), 1.98 (app t, *J* = 2.5 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 203.5, 159.5, 129.8, 129.2, 113.8, 85.6, 81.9, 72.8, 70.4, 55.2, 34.0, 21.3, 15.3; IR (neat) 3292, 2967, 2837, 1731, 1515, 1249 cm^{-1}; HRMS (ES+) *m/z* for $C_{15}H_{18}O_3Na$ $[M+Na]^+$ calcd 269.1154, found 269.1147.

(3*R*,4*S*,5*R*,6*R*)-3-(Dimethylphenylsilanyl)-5-(4-methoxy-benzyloxy)-6-methyl-non-1-en-8-yn-4-ol (21)

To a −78 °C slurry of aldehyde **19** (5.95 g, 24.2 mmol) and 4Å mol. sieves (4.8 g) in toluene (20 mL) was added (*S*,*S*)-**20**[27] (61 mL of a 1.0M solution in toluene, 60.4 mmol). The reaction was stirred at −78 °C for 18 h and then quenched with 2N NaOH aq. (100 mL). The biphasic mixture was filtered through Celite and extracted with EtOAc (30 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford **21** (9.19 g, 90%) as a colorless oil: $[\alpha]^{25}_D = -6°$ (*c* 2.48, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 7.55-7.57 (m, 2H), 7.34-7.36 (m, 3H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.98 (dt, *J* = 10.4, 21.5 Hz, 1H),

5.03 (d, *J* = 10.4 Hz, 1H), 4.85 (d, *J* = 21.5 Hz, 1H), 4.58 (d, *J* = 13.0 Hz, 1H), 4.49 (d, *J* = 13.5 Hz, 1H), 3.81 (s, 3H), 3.73-3.77 (m, 1H), 3.31 (dd, *J* = 3.2, 6.8 Hz, 1H), 2.43 (d, *J* = 4.0 Hz, 1H), 2.08-2.18 (m, 1H), 1.91-1.98 (m, 3H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.39 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.3, 137.9, 134.8, 134.1, 130.4, 129.4, 129.0, 127.6, 114.5, 113.9, 85.5, 83.6, 74.9, 71.1, 69.3, 55.3, 39.2, 34.1, 20.3, 17.9, -3.8, -4.2; IR (neat) 3560, 3304, 2961, 1613, 1514 cm^{-1}; HRMS (ES+) *m/z* for $C_{26}H_{34}O_3SiNa$ $[M+Na]^+$ calcd 445.2175, found 445.2176.

1-[(1*R*,2*S*,3*R*)-3-(Dimethyl-phenyl-silanyl)-1-((*R*)-1-methyl-but-3-ynyl)-2-triethylsilanyloxy-pent-4-enyloxymethyl]-4-methoxy-benzene (7)

To a solution of 21 (1.01 g, 2.39 mmol) in DMF (2.5 mL) was added imidazole (0.50 g, 7.4 mmol) and triethylsilylchloride (1.21 mL, 7.17 mmol). The reaction was heated to 45 °C for 17 h and then quenched with water (15 mL) and extracted with Et_2O (25 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford **7** (1.19 g, 93%) as a colorless oil: $[\alpha]^{25}_D$ = +31° (*c* 1.30, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.49-7.52 (m, 2H), 7.29-7.35 (m, 3H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.12 (dt, *J* = 10.8, 17.2 Hz, 1H), 4.91 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.79 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.30 (AB, *J* = 18.8 Hz, 1H), 4.27 (d, *J* = 12.4 Hz, 1H), 4.50-4.70 (m, 1H), 3.81 (s, 3H), 3.22 (dd, *J* = 3.6, 8.4 Hz, 1H), 2.31-2.36 (m, 2H), 2.19 (dt, *J* = 3.2, 16.8 Hz, 1H), 2.09-2.13 (m, 1H), 1.94 (app t, *J* = 2.4 Hz, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.91 (t, *J* = 8.4 Hz, 9H), 0.50-0.57 (m, 6H), 0.34 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.1, 138.0, 136.5, 134.3, 130.8, 129.3, 128.9, 127.6, 113.6, 113.2, 85.3, 83.4, 72.6, 71.5, 69.5, 55.2, 37.0, 32.9, 22.8, 17.0, 7.1, 5.6, -3.2, -4.2; IR (neat) 3309, 2956, 2877, 1613, 1514, 1248 cm^{-1}; HRMS (ES+) *m/z* for $C_{32}H_{48}O_3Si_2Na$ $[M+Na]^+$ calcd 559.3040, found 559.3044.

(4*R*,5*R*)-4-((*E*)-4-{(2*S*,4*S*,5*R*)-4-(Dimethyl-phenyl-silanyl)-5-[(1*S*,2*R*,3*R*)-2-(4-methoxy-benzyloxy)-3-methyl-1-triethylsilanyloxy-hex-5-ynyl]-tetrahydro-furan-2-yl}-but-1-enyl)-2,2-dimethyl-5-vinyl-[1,3]dioxolane (24)

A 25-mL round bottom flask was charged with aldehyde 5 (1.06 g, 5.04 mmol), allylsilane 7 (8.12 g, 15.1 mmol), activated 4 Å molecular sieves (2.0 g) and dichloromethane (10 mL). The slurry was stirred at room temperature for 10 min and then cooled to −78 °C. The cooled reaction was then treated with $BF_3{\cdot}OEt_2$ (0.64 mL, 5.04 mmol, freshly distilled from calcium hydride). The reaction mixture was stirred at −78 °C for 21 h and then quenched with triethylamine (1 mL). The mixture was diluted with sat. aq. $NaHCO_3$ (60 mL) and Et_2O (50 mL) and filtered through Celite. The aqueous phase was extracted with Et_2O (30 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography afforded **24** (1.19 g, 48%; (6.27 g of allylsilane **7** was recovered)) as a colorless oil with >20:1 diastereoselectivity: $[\alpha]^{25}_D$ = +23° (*c* 0.76, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 (app dd, *J* = 1.6, 7.2 Hz, 2H), 7.29-7.38 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.74-5.82 (m, 2H), 5.41 (b dd, *J* = 7.2, 15.2 Hz, 1H), 5.32 (d, *J* = 17.6 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.51 (d, *J* = 10.8 Hz, 1H), 4.39 (d, *J* = 10.8 Hz, 1H), 4.05 (app dd, *J* = 6.8, 12.4 Hz, 3H), 3.81 (s, 3H), 3.71 (m, 1H), 3.58 (d, *J* = 5.6 Hz, 1H), 3.32 (app t, *J* = 6.8 Hz, 1H), 2.03-2.34 (m, 5H), 1.94 (t, *J* = 2.4 Hz, 1H), 1.79-1.83 (m, 1H), 1.58-1.69 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.51-0.61 (m, 6H), 0.32 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 158.9, 137.6, 136.4, 134.3, 133.8, 130.9, 129.1, 128.9, 127.8, 125.5, 118.2, 113.2, 108.6, 83.8, 83.2, 82.1, 80.2, 78.5, 77.2, 73.6, 73.1, 69.2, 55.1, 35.2, 34.5. 34.3, 29.3, 27.0, 26.9, 26.2, 22.1, 17.1, 7.1, 5.2, -4.1; IR (neat) 3309, 2955, 2250, 2115, 1614, 1514 cm^{-1}; HRMS (ES+) *m/z* for $C_{44}H_{66}O_6Si_2Na$ $[M+Na]^+$ calcd 769.4296, found 769.4307.

(1*S*,2*R*,3*R*)-1-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-3-methyl-1-triethylsilanyloxy-hex-5-yn-2-ol (25)

To a solution of [3+2] adduct 24 (1.81 g, 2.42 mmol) in DMF (2.5 mL) was added TBAF•3H_2O (3.82 g, 12.1 mmol). The reaction was fitted with a condenser and placed in a 90 °C oil bath for 72 h. Additional TBAF•3H_2O (2.0 g, 6.34 mmol) was added to the reaction three times during the 72 h period; at hour 8, hour 32 and hour 56. After 72 h, the reaction was diluted with pH 7 buffer (50 mL) and Et_2O (30 mL). The aqueous phase was extracted with Et_2O (30 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford the alcohol product (1.03 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ = +6.4° (*c* 0.39, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.73-5.81 (m, 2H), 5.41 (app bddd, *J* = 1.6, 6.0, 15.6 Hz, 1H), 5.32 (d, *J* = 16.4 Hz, 1H), 5.21 (dd, *J* = 1.2, 10.4 Hz, 1H), 4.58 (app q, *J* = 10.8 Hz, 2H), 4.03 (app q, *J* = 6.8 Hz, 2H), 3.93 (app q, *J* = 7.2 Hz, 1H), 3.85 (quint., *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 3.45-3.50 (m, 1H), 3.35 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.23 (bd, *J* = 6.8 Hz, 1H), 2.34 (ddq, *J* = 2.4, 6.8, 16.8 Hz, 2H), 2.05-2.24 (m, 3H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.89-1.95 (m, 1H), 1.78-1.86 (m, 1H), 1.64-1.75 (m, 2H), 1.46-1.60 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.2, 135.9, 134.2, 130.4, 129.5, 125.9, 118.4, 113.6, 108.7, 83.1, 82.1, 82.0, 81.6, 80.4, 79.2, 73.5, 73.1, 69.9, 55.1, 35.1, 34.2, 31.0, 29.0, 27.0, 27.0, 21.8, 16.2; IR (neat) 3536, 3296, 2984, 2934, 1613, 1514, 1248 cm^{-1}; HRMS (ES+) *m/z* for $C_{30}H_{42}O_6Na$ $[M+Na]^+$ calcd 521.2879, found 521.2879.

To a 0 °C solution of the alcohol from the preceding step (1.2 g, 2.41 mmol) and triethylamine (0.67 mL, 4.82 mmol) in dichloromethane (8 mL) was added triethylsilyl trifluoromethanesulfonate (0.65 mL, 2.89 mmol). After 5 min the reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and Et_2O (30 mL). The aqueous phase was extracted with Et_2O (30 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford the triethylsilyl ether (1.39 g, 94%) as a colorless oil: $[\alpha]^{25}_D$ = +11° (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.75-5.85 (m, 2H), 5.44 (bdd, *J* = 7.2, 15.2 Hz, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.23 (dd, *J* = 0.8, 10.4 Hz, 1H), 4.55 (s, 2H), 4.05 (app q, *J* = 6.4 Hz, 2H), 3.93 (app q, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.75-3.79 (m, 1H), 3.74 (dd, *J* = 3.2, 6.8 Hz, 1H), 3.29 (dd, *J* = 3.2, 8.8 Hz, 1H), 2.28-2.40 (m, 2H), 2.09-2.24 (m, 3H), 1.97 (t, *J* = 2.8 Hz, 1H), 1.79-1.94 (m, 2H), 1.61-1.70 (m, 2H), 1.51-1.59 (m, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.55-0.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.3, 134.3, 131.0, 129.0, 125.7, 118.4, 113.6, 108.8, 83.2, 83.1, 82.2, 82.2, 80.4, 78.2, 75.8, 71.9, 69.6, 55.2, 35.3, 33.2, 31.1, 29.2, 27.8, 27.0, 26.9, 22.5, 16.5, 7.0, 5.2; IR (neat) 3308, 2954, 2875, 1612, 1514, 1247, 1057 cm^{-1}; HRMS (ES+) *m/z* for $C_{36}H_{56}O_6SiNa$ $[M+Na]^+$ calcd 635.3744, found 635.3754.

To a 0 °C solution of the triethylsilyl ether (0.621 g, 1.01 mmol) in dichloromethane (10 mL) and pH 7 buffer (1 mL) was added DDQ (0.46 g, 2.02 mmol). The reaction was stirred for 1 h, and then quenched with sat. aq. $NaHCO_3$ (40 mL) and Et_2O (30 mL). The aqueous phase was extracted with Et_2O (30 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography afforded **25** (0.49 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ = +13° (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.83 (m, 2H), 5.43 (app bddd, *J* = 1.2, 6.0, 15.2 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.23 (dd, *J* = 0.8, 10.4 Hz, 1H), 4.05 (app q, *J* = 6.4 Hz, 2H), 3.76 (m, 2H), 3.67 (d, *J* = 7.2 Hz, 1H), 3.18 (t, *J* = 9.6 Hz, 1H), 2.50 (d, *J* = 9.6 Hz, 1H), 2.48 (dt, *J* = 3.6, 16.4 Hz, 1H), 2.08-2.20 (m, 2H), 1.95 (t, *J* = 2.4 Hz, 1H), 1.84-1.97 (m, 2H), 1.74-1.80 (m, 1H), 1.61-1.66 (m, 1H), 1.59-1.46 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.66 (app dsept., *J* = 7.6, 19.2 6H); ^{13}C NMR (100MHz,

$CDCl_3$) δ 136.2, 134.3, 125.9, 118.5, 108.8, 83.1, 82.2, 82.2, 81.3, 78.7, 74.5, 74.4, 69.3, 35.7, 35.2, 30.8, 29.2, 27.4, 27.1, 27.0, 22.1, 15.7, 7.0, 5.3; IR (neat) 3524, 3310, 2954, 2875, 1379, 1238, 1054 cm^{-1}; HRMS (ES+) *m/z* for $C_{28}H_{48}O_5SiNa$ $[M+Na]^+$ calcd 515.3169, found 515.3171.

(4*R*,5*S*)-4-Methyl-3-((*E*)-(*R*)-2-methyl-hexa-3,5-dienoyl)-5-phenyl-oxazolidin-2-one (36)

To a −78 °C solution of oxazolidinone **35**[39] (8.75 g, 32.2 mmol) in THF (90 mL) was added NaHMDS (8.28 g, 45.1 mmol) in THF (10 mL). The reaction was stirred at −78 °C for 1 h and then treated with methyl trifluoromethanesulfonate (5.47 mL, 48.4 mmol). The reaction was quenched after 3 h with sat. aq. NH_4Cl (100 mL) and Et_2O (50 mL). The aqueous phase was extracted with Et_2O (50 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Analysis of the crude product by ^1H NMR indicated a 5:1 mixture of diastereomers in favor of **36**. The crude product was purified by flash column chromatography in 20% Et_2O/hexane (minor isomer, R_f = 0.21; major isomer, R_f = 0.36) to afford **36** (7.30 g, 79%) as a colorless oil: $[\alpha]^{25}_D$ = −27° (*c* 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.44 (m, 3H), 7.30-7.32 (m, 2H), 6.20-6.37 (m, 2H), 5.83 (dd, *J* = 8.4, 15.2 Hz, 1H), 5.66 (d, *J* = 7.2 Hz, 1H), 5.21 (app d, *J* = 17.6 Hz, 1H), 5.09 (app d, *J* = 10.8 Hz, 1H), 4.53 (quint., *J* = 7.6 Hz, 1H), 4.74 (quint., *J* = 6.8 Hz, 1H), 1.33 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.4, 152.6, 136.5, 133.2, 132.7, 132.6, 128.7, 128.7, 125.6, 117.3, 78.8, 55.1, 40.8, 17.3, 14.5; IR (neat) 2981, 2934, 1782, 1699, 1356, 1197 cm^{-1}; HRMS (ES+) *m/z* for $C_{17}H_{21}NO_4Na$ $[M+Na]^+$ calcd 308.1263, found 308.1262.

Tricarbonyl[(4*R*,5*S*)-4-Methyl-3-((*E*)-(2*S*,3*R*)-2-methyl-hexa-3,5-dienoyl)-5-phenyl-oxazolidin-2-one]iron (38) and Tricarbonyl[(4*R*,5*S*)-4-Methyl-3-((*E*)-(2*S*,3*S*)-2-methyl-hexa-3,5-dienoyl)-5-phenyl-oxazolidin-2-one]iron (37)

To a solution of oxazolidinone 36 (2.0 g, 7.0 mmol) in benzene (23 mL) was added diiron (nonacarbonyl) (3.8 g, 10.5 mmol). The reaction was fitted with a condenser and refluxed for a total of 24 h. Additional diiron(nonacarbonyl) (1.5 g, 4.12 mmol) and benzene (10 mL) was added to the reaction at hour 6 and hour 20. After 24 hours, the reaction was cooled to room temperature, filtered through Celite with an Et_2O (25 mL) wash and concentrated to afford a 1:1 mixture of **38** and **37**. The crude product mixture was separated by flash column chromatography (10% Et_2O/hexanes to 40% Et_2O/hexanes with **37** (0.78 g) eluting before **38** (0.71 g), **38** and **37** combined yield of 50%).

Data for **38** (yellow solid): R_f = 0.33 (30% Et_2O/hexane); $[\alpha]^{25}_D$ = +8° (*c* 0.1, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 7.36-7.45 (m, 3H), 7.36 (app d, *J* = 6.8 Hz, 2H), 5.71 (d, *J* = 7.2 Hz, 1H), 5.46 (dd, *J* = 4.8, 8.4 Hz, 1H), 5.22-5.27 (m, 1H), 4.76 (quint., *J* = 6.8 Hz, 1H), 3.82-3.40 (m, 1H), 1.78 (app dd, *J* = 1.6, 6.8 Hz, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.15 (app t, *J* = 8.8 Hz, 1H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.39 (app dd, *J* = 2.0, 9.6 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 210.8, 175.2, 152.9, 133.2, 128.9, 128.8, 125.7, 86.4, 81.9, 78.9, 64.7, 55.1, 41.0, 40.4, 19.9, 14.5; IR (neat) 2984, 2047, 1970, 1779, 1697, 1355 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{19}FeNO_6Na$ $[M+Na]^+$ calcd 448.0459, found 448.0464.

Data for **37** (yellow solid): R_f = 0.50 (30% Et_2O/hexane); $[\alpha]^{25}_D$ = −83° (*c* 0.1, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 7.30-7.45 (m, 5H), 5.71 (d, *J* = 7.2 Hz, 1H), 5.28-5.33 (m, 2H), 4.84 (quint., *J* = 6.8 Hz, 1H), 3.65-3.78 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.36 (app dd, *J* = 7.6, 10.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.45 (app dd, *J* = 2.8, 8.8 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 211.4, 174.6, 152.6, 133.2, 128.7, 125.6, 87.1, 82.7, 79.2, 62.9, 55.4, 43.4, 40.4, 26.3, 22.3, 14.3; IR (neat) 2977, 2046, 1978, 1782, 1700, 1342 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{19}FeNO_6Na$ $[M+Na]^+$ calcd 448.0459, found 448.0462.

Tricarbonyl[(*E*)-(2*S*,3*R*)-2-Methyl-hexa-3,5-dienoic acid]iron (9)

To a 0 °C solution of oxazolidinone **38** (1.15 g, 2.70 mmol) in THF (21 mL) and water (7 mL) was added LiOH (0.194 g, 8.11 mmol). The reaction was stirred for 1.5 h and then quenched with 1M HCl (25 mL) and Et_2O (25 mL). The aqueous phase was extracted with Et_2O (25 mL × 3). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude carboxylic acid was purified by flash column chromatography to afford **9** (0.423 g, 58%) as a yellow solid: $[\alpha]^{25}_D$ = +11° (*c* 0.1, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 10.40 (bs, 1H), 5.38-5.44 (m, 1H), 5.25-5.30 (m, 1H), 2.32 (bs, 1H), 1.81 (d, *J* = 6.4 Hz, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 0.94 (app t, *J* = 9.2 Hz, 1H), 0.38 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 181.1, 87.1, 82.3, 63.1, 44.0, 40.5, 19.0; IR (neat) 2983, 2049, 1971, 1705 cm^{-1}; HRMS (EI+) *m/z* for $C_9H_{10}FeO_4$ $[M\text{-}CO]^+$ calcd 237.9928, found 237.9918. The spectroscopic data obtained for **9** were fully consistent with data for racemic **9** previously published by Donaldson.[40]

Tricarbonyl[(*E*)-(2*S*,3*S*)-2-Methyl-hexa-3,5-dienoic acid]iron (10)

To a room temperature solution of oxazolidinone **37** (1.08 g, 2.54 mmol) in THF (18 mL) and water (6 mL) was added LiOH (0.304 g, 12.7 mmol). The reaction was stirred for 6.5 h and then quenched with 1M HCl (25 mL) and Et_2O (25 mL). The aqueous phase was extracted with Et_2O (25 mL × 3). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude carboxylic acid was purified by flash column chromatography to afford **10** (0.421 g, 62%) as a yellow solid: $[\alpha]^{25}_D$ = −140° (*c* 0.39, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 11.26 (bs, 1H), 5.22-5.30 (m, 2H), 2.37-2.45 (m, 1H), 1.74-1.78 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.05 (app dd, *J* = 8.0, 10.0 Hz, 1H), 0.36 (app dd, *J* = 4.4, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 181.0, 86.4, 82.2, 62.1, 45.2, 39.8, 21.4; IR (neat) 2979, 2934, 2049, 1974,1708 cm^{-1}; HRMS (EI+) *m/z* for $C_9H_{10}FeO_4$ $[M\text{-}CO]^+$ calcd 237.9928, found 237.9924.

(*E*)-(*R*)-2-Methyl-hexa-3,5-dienoic acid (13)

To a 0 °C solution of oxazolidinone **36** (0.536 g, 1.88 mmol) and 30 % (w/w) H_2O_2 (2.3 mL, 22.6 mmol) in THF (6.3 mL) was added LiOH (0.24 g, 5.6 mmol). The reaction was stirred for 1.5 h and then quenched with 1M HCl (20 mL) and Et_2O (20 mL). The aqueous phase was extracted with Et_2O (20 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford **13** (0.151 g, 64 %): $[\alpha]^{25}_D$ = −47° (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.07 (bs, 1H), 6.34 (dt, *J* = 10.5, 17.0 Hz, 1H), 6.17 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.77 (dd, *J* = 8.0, 15.5 Hz, 1H), 5.20 (d, *J* = 18.0 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 3.22 (quint., *J* = 7.5 Hz, 1H), 1.32 (d, *J* = 7.0 Hz, 3H),; ^{13}C NMR (100MHz, $CDCl_3$) δ 181.1, 136.4, 132.6, 132.0, 118.1, 117.4, 42.6, 17.0; IR (neat) 3088, 2980, 1709, 1414, 1212, 1003 cm^{-1}; HRMS (ESI-TOF) *m/z* for $C_7H_{10}NO_2Na$ $[M\text{-}H]^-$ calcd 125.0608, found 125.0607.

2-*epi*-Amphidinolide E (2) series

Tricarbonyl[(*E*)-(2*R*,3*S*)-2-Methyl-hexa-3,5-dienoic acid (1*R*,2*R*)-1-((*R*)-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-triethylsilanyloxy-methyl)-2-methyl-pent-4-ynyl ester]iron (39)

To 0 °C solution of 25 (0.435 g, 0.883 mmol), 10 (0.332 g, 1.24 mmol), triethylamine (0.37 mL, 2.65 mmol), and DMAP (0.108 g, 0.883 mmol) in THF (1.8 mL) was added 2,4,6-trichlorobenzoyl chloride (0.19 mL, 1.24 mmol). The reddish brown solution was stirred at 0 °C for 1 h and allowed to warm to room temperature over another 1 h. After complete consumption of 25 was observed by TLC analysis, the reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and Et_2O (30 mL). The aqueous phase was extracted with Et_2O (25 mL ×

3). The organic phase was washed with sat. aq. NH_4Cl, brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography afforded **39** (0.614 g, 94%) as a colorless oil: $[\alpha]^{25}_D = -3.8°$ (*c* 0.87, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 5.75-5.85 (m, 2H), 5.40-5.48 (m, 1H), 5.35-5.39 (m, 1H), 5.33 (d, *J* = 16.4 Hz, 1H), 5.22-5.29 (m, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.72 (d, *J* = 8.8 Hz, 1H), 4.03-4.08 (m, 2H), 3.67-3.78 (m, 1H), 3.69 (dd, *J* = 2.0, 7.2 Hz, 1H), 3.58 (app q, *J* = 6.8 Hz, 1H), 2.00-2.34 (m, 7H), 1.96 (t, *J* = 2.4 Hz, 1H), 1.77-1.94 (m, 3H), 1.59-1.69 (m, 1H), 1.50-1.59 (m, 1H), 1.40-1.50 (m, 1H), 1.44 (s, 3H), 1.44 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.92-1.02 (m, 1H), 0.96 (t, *J* = 7.6 Hz, 9H), 0.57-0.73 (m, 6H), 0.35 (b d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 211.1, 173.5, 135.9, 134.2, 125.9, 118.2, 108.7, 87.0, 82.2, 82.1, 82.1, 80.4, 78.4, 77.3, 75.1, 69.7, 63.8, 44.5, 40.3, 35.1, 33.3, 30.8, 29.1, 27.6, 27.0, 27.0, 22.0, 19.3, 16.1, 6.9, 5.3; IR (neat) 3311, 2954, 2050, 1980, 1732, 1237 cm^{-1}; HRMS (ES+) *m/z* for $C_{38}H_{56}FeO_9SiNa$ $[M+Na]^+$ calcd 763.2941, found 763.2955.

(*E*)-(*S*)-2-Methyl-hexa-3,5-dienoic acid (1*R*,2*R*)-1-((*R*)-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-triethylsilanyloxy-methyl)-2-methyl-pent-4-ynyl ester (73)

To a 0 °C solution of 39 (0.574 g, 0.775 mmol) in acetone (8 mL) was added cerium ammonium nitrate (CAN) (0.935 g, 1.70 mmol). The reaction was stirred for 1.5 h, then quenched with triethylamine (2 mL) and diluted with sat. aq. $NaHCO_3$ (50 mL) and Et_2O (50 mL). The aqueous phase was extracted with Et_2O (30 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford **73** (0.447 g, 96%) as a colorless oil: $[\alpha]^{25}_D = +22°$ (*c* 0.98, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 6.31 (dt, *J* = 10.0, 17.2, 1H), 6.15 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.72-5.85 (m, 3H), 5.40-5.49 (m, 1H), 5.33 (d, *J* = 16.4 Hz, 1H), 5.23 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 16.2, 1H), 5.07 (d, *J* = 11.2 Hz, 1H), 4.73 (app dd, *J* = 2.4, 8.8 Hz, 1H), 4.02-4.08 (m, 2H), 3.57-3.77 (m, 3H), 3.21 (quint., *J* = 7.2 Hz, 1H), 1.96-2.26 (m, 5H), 1.94 (t, *J* = 2.4 Hz, 1H), 1.77-1.98 (m, 2H), 1.58-1.68 (m, 1H), 1.37-1.58 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.57-0.73 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.4, 136.2, 135.8, 134.2, 132.3, 132.1, 125.8, 118.1, 116.8, 108.6, 82.1, 82.1, 82.0, 80.3, 78.3, 77.2, 75.1, 69.6, 42.9, 35.0, 33.2, 30.8, 29.0, 27.5, 26.9, 26.8, 21.8, 17.0, 16.0, 6.8, 5.2; IR (neat) 3311, 2953, 2876, 2050, 1983, 1738, 1732, 1240 cm^{-1}; HRMS (ES+) *m/z* for $C_{35}H_{56}O_6SiNa$ $[M+Na]^+$ calcd 623.3744, found 623.3737.

(4*E*,11*E*,13*E*)-(1*S*,6*R*,10*R*,15*S*,18*R*,19*R*,20*S*)-8,8,15-Trimethyl-18-((*R*)-1-methyl-but-3-ynyl)-19-triethylsilanyloxy-7,9,17,23-tetraoxa-tricyclo[18.2.1.$0^{6,10}$]tricosa-4,11,13-trien-16-one (40)

To a solution of polyene 73 (50 mg, 0.083 mmol) in dichloromethane (83 mL) was added Grubbs' first generation catalyst (14 mg, 0.017 mmol) in dichloromethane (2 mL). The reaction was fitted with a condenser, refluxed for 18 h and condensed. The crude product was purified by flash column chromatography to afford 40 (29 mg, 60%) as a colorless oil. In addition, an inseparable mixture of products thought to arrive by enyne metathesis (7 mg, 15%) was also isolated. Spectroscopic data for **40**: $[\alpha]^{25}_D = -57°$ (*c* 0.57, $CHCl_3$); ^1H NMR (400MHz, $CDCl_3$) δ 6.15-6.26 (m, 2H), 5.93 (dd, *J* = 4.8, 14.8 Hz, 1H), 5.71 (ddd, *J* = 3.6, 9.6, 15.2 Hz, 1H), 5.56 (dd, *J* = 8.4, 14.0 Hz, 1H), 5.34 (dd, *J* = 8.0, 14.8 Hz, 1H), 4.55 (d, *J* = 9.2 Hz, 1H), 4.03 (dt, *J* = 8.8, 21.2 Hz, 2H), 3.68 (d, *J* = 8.4 Hz, 1H), 3.28-3.37 (m, 1H), 3.18-3.28 (m, 2H), 2.19-2.36 (m, 3H), 1.82-2.03 (m, 3H), 1.62-1.73 (m, 1H), 1.40-1.55 (m, 2H), 1.43 (s, 6H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.13-1.28 (m, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.53-0.70 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.5, 138.1, 135.9, 134.6, 128.9, 127.5, 125.9, 109.0, 83.1, 82.8, 82.2, 79.9, 78.5, 77.2, 75.0, 69.4, 43.3, 33.1, 32.1, 29.6, 28.5, 27.2, 27.1, 27.1, 22.3, 15.5, 12.0, 7.1, 5.6; IR (neat) 3310, 2935, 2874, 1726, 1238, 1052 cm^{-1}; HRMS (ES+) *m/z* for $C_{33}H_{52}O_6SiNa$ $[M+Na]^+$ calcd 595.3431, found 595.3438.

(4*E*,11*E*,13*E*)-(1*S*,6*R*,10*R*,15*S*,18*R*,19*R*,20*S*)-18-((*R*)-3-Iodo-1-methyl-but-3-enyl)-8,8,15-trimethyl-19-triethylsilanyloxy-7,9,17,23-tetraoxa-tricyclo[18.2.1.$0^{6,10}$]tricosa-4,11,13-trien-16-one (41)

To a 0 °C solution of *i*-Pr_2NH (0.45 mL, 3.2 mmol) in THF (3 mL) was added *n*-BuLi (1.24 mL of a 2.41M solution in hexanes, 3.0 mmol). The reaction was allowed to stir for 30 min and then cooled to −30 °C. To this mixture was added Bu_3SnH (0.80 mL, 3.0 mmol). After 1h, Et_2AlCl (1.7 mL of a 1.8M solution in toluene, 3.0 mmol) was added. The reaction was stirred at −30 °C for another 1.5 h and then used immediately in the stannylalumination-protonolysis of **40**.

To a −30 °C solution of **40** (23 mg, 0.40 mmol) in THF (1 mL) was added Bu_3Sn-$AlEt_2$ (0.57 mL of the 0.42M solution from above, 0.24 mmol), followed by CuCN (1 mg, 0.012 mmol). The bright orange solution was stirred for 1 h at −30 °C, then quenched with sat. aq. NH_4Cl (20 mL) and Et_2O (20 mL). This mixture was stirred vigorously at room temp for 15 min. The aqueous phase was extracted with Et_2O (10 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography afforded the vinylstannane product (18 mg, 51%) as a colorless oil: $[\alpha]^{25}_D$ = −78° (*c* 0.12, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.15-6.28 (m, 2H), 5.96 (dd, *J* = 4.8, 14.4 Hz, 1H), 5.72 (ddd, *J* = 3.2, 9.2, 15.2 Hz, 1H), 5.64 (app t, $^3J_{Sn\text{-}H}$ = 69.2 Hz, 1H), 5.57 (dd, *J* = 8.4, 14.0 Hz, 1H), 5.34 (dd, *J* = 8.4, 15.2 Hz, 1H), 5.16 (app t, $^3J_{Sn\text{-}H}$ = 31.6 Hz, 1H), 4.49 (d, *J* = 10.0 Hz, 1H), 4.04 (app dt, *J* = 8.8, 20.4 Hz, 1H), 3.74 (d, *J* = 8.4 Hz, 1H), 3.28-3.36 (m, 1H), 3.18-3.28 (m, 2H), 2.28-2.40 (m, 3H), 1.82-2.13 (m, 4H), 1.62-1.74 (m, 1H), 1.40-1.55 (qm, 7H), 1.44 (s, 6H), 1.13-1.38 (m, 11H), 0.85-1.00 (m, 24H), 0.79 (d, *J* = 6.4 Hz, 3H), 0.55-0.70 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.6, 153.9, 138.2, 136.0, 134.9, 131.1, 128.7, 127.3, 127.0, 125.8, 109.0, 83.1, 82.3, 80.1, 79.9, 74.9, 45.3, 43.3, 32.7, 32.1, 29.6, 29.2, 29.1, 29.0, 28.5, 27.4, 27.2, 27.1, 14.8, 13.7, 12.0, 9.5, 7.1, 5.6; IR (neat) 2955, 1727, 1378, 1239, 1052 cm^{-1}; HRMS (ES+) *m/z* for $C_{45}H_{80}O_6SiSnNa$ $[M+Na]^+$ calcd 887.4644, found 887.4666.

To a −45 °C solution of the vinylstannane from the preceding step (20 mg, 0.023 mmol) in dichloromethane (1 mL) was added NIS (6 mg, 0.03 mmol). The reaction was stirred at −45 °C for 1 h and then quenched with sat. aq. $Na_2S_2O_3$ (30 mL) and extracted with Et_2O (20 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford **41** (15 mg, 93%) as a colorless oil: $[\alpha]^{25}_D$ = −72° (*c* 0.43, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.17-6.27 (m, 2H), 6.02 (s, 1H), 5.93 (dd, *J* = 5.2, 14.4 Hz, 1H), 5.73 (ddd, *J* = 3.6, 9.6, 15.2 Hz, 1H), 5.72 (s, 1H), 5.58 (dd, *J* = 8.8, 14.0 Hz, 1H), 5.34 (dd, *J* = 8.4, 15.2 Hz, 1H), 4.55 (d, *J* = 9.6 Hz, 1H), 4.03 (app dt, *J* = 8.8, 23.6 Hz, 2H), 3.72 (d, *J* = 8.4 Hz, 1H), 3.28-3.35 (m, 1H), 3.19-3.28 (m, 2H), 2.29-2.50 (m, 3H), 1.82-2.05 (m, 3H), 1.65-1.73 (m, 1H), 1.45-1.57 (m, 1H), 1.43 (s, 6H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.12-1.27 (m, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.56-0.72 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.8, 138.1, 136.0, 134.5, 129.0, 127.5, 127.0, 125.8, 111.5, 109.0, 83.1, 82.2, 80.0, 78.6, 74.9, 48.3, 43.3, 32.8, 32.0, 29.6, 28.5, 27.2, 27.1, 27.1, 14.6, 12.0, 7.2, 5.7; IR (neat) 2933, 2873, 1723, 1239, 1052 cm^{-1}; HRMS (ES+) *m/z* for $C_{33}H_{53}IO_6SiNa$ $[M+Na]^+$ calcd 723.2554, found 723.25563

2-*epi*-amphidinolide E (2)

A solution of vinyl iodide **41** (44 mg, 0.063 mmol) in a mixture of AcOH, THF and water (4/1/1 ratio) (1.5 mL) was heated to 40 °C for 7h. The mixture was then carefully poured into a separatory funnel containing Et_2O (40 mL) and sat. aq. $NaHCO_3$ (60 mL). The pH of the aqueous layer was adjusted to ~7 using solid $NaHCO_3$. The aqueous phase was extracted with Et_2O (20 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$,

filtered and concentrated. Analysis of the crude product by ^{1}H NMR indicated a 10:1 mixture of the desired C(18) and undesired C(17) lactones.

To the crude mixure of vinyl iodide-containing lactones (from above) and CuCl (23 mg, 0.23 mmol) in THF (0.5 mL) was added vinylstannane **6**[12] (78 mg, 0.21 mmol), followed by Pd $(PPh_3)_4$ (10 mg, 0.0084 mmol) in THF (0.5 mL). The reaction was stirred at room temperature for 26 h, and then diluted with Et_2O (30 mL), filtered through Celite and concentrated. The crude product was purified by flash column chromatography using 10% methanol/chloroform to afford material that was still contaminated with an organotin impurity. The stannane impurity was removed by HPLC purification with 100% ethyl acetate eluent on a normal phase, Varian Dynamax Microsorb 60-8 Si, 250 × 21.4 mm column. The retention time for 2-*epi*-amphidinolide E was 8 min. The flow rate was 18 mL/min. 2-*epi*-amphidinolide E was detected using UV absorption (λ = 254 nm and 280 nm) and RI detection. Using the above conditions 11 mg (34% from **41**) of pure 2-*epi*-amphidinolide E (**2**) was isolated: $[\alpha]^{25}_D = -80°$ (*c* 0.15, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.14-6.25 (m, 2H), 6.04 (d, *J* = 16.0 Hz, 1H), 5.95-6.04 (m, 1H), 5.54-5.74 (m, 3H), 5.30 (dd, *J* = 7.2, 15.2 Hz, 1H), 4.98 (s, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 4.70 (s, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 3.95 (app dt, *J* = 8.4, 19.2 Hz, 2H), 3.69 (app t, *J* = 5.2 Hz, 1H), 3.46-3.53 (m, 1H), 3.40-3.46 (m, 1H), 3.35 (quint., *J* = 5.2 Hz, 1H), 2.72-2.84 (m, 2H), 2.22-2.48 (m, 5H), 1.60-1.95 (m, 5H), 1.72 (s, 3H), 1.25-1.52 (m, 4H), 1.34 (d, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.9, 144.7, 144.1, 134.8, 134.2, 134.1, 133.4, 131.2, 129.7, 129.6, 128.2, 116.1, 110.9, 79.9, 78.7, 77.9, 77.3, 76.6, 73.2, 43.1, 41.5, 36.3, 32.8, 32.3, 30.2, 29.1, 27.5, 22.7, 15.5, 13.4; IR (neat) 3413, 2933, 1723, 1454, 1238, 992 cm^{-1}; HRMS (ES+) *m/z* for $C_{30}H_{44}O_6Na$ $[M+Na]^+$ calcd 523.3036, found 523.3016.

Synthesis of 19-*epi*-series Precursors

(1*R*,2*S*)-1-((*S*)-2,2-Diethyl-[1,3]dioxolan-4-yl)-2-methyl-but-3-en-1-ol (60)

To a −78 °C slurry of L-glyceraldehyde pentylidene ketal **58**[24] (12.1 g, 76.5 mmol) and 4Å mol. sieves (9 g) in toluene (100 mL) was added *Z*-(*S*,*S*)-crotylboronate **59**[23] (153 mL of a 1.0M solution in toluene, 153 mmol). The reaction was stirred at −78 °C for 18 h and then quenched with 2N NaOH aq. (300 mL). The biphasic mixture was filtered through Celite and extracted with EtOAc (75 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography to afford **60** (15.4 g, 94%) as a colorless oil: $[\alpha]^{25}_D = -45°$ (*c* 4.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, *J* = 8.0, 10.0, 17.2 Hz, 1H), 5.04 (d, *J* = 10.0 Hz, 1H), 5.00 (s, 1H), 4.00-4.08 (m, 1H), 3.94 (app t, *J* = 7.6 Hz, 1H), 3.81 (app t, *J* = 7.6 Hz, 1H), 3.60-3.66 (m, 1H), 2.18-2.28 (m, 2H), 1.52-1.68 (m, 4H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.80-0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 115.4, 112.4, 76.8, 73.8, 65.1, 40.7, 29.1, 15.3, 8.2, 7.9; IR (neat) 3481, 2974, 1641, 1463 cm^{-1}; HRMS (ES+) *m/z* for $C_{12}H_{22}O_3Na$ $[M+Na]^+$ calcd 237.1467, found 237.1460.

(3*S*,4*R*)-4-((*S*)-2,2-Diethyl-[1,3]dioxolan-4-yl)-4-(4-methoxy-benzyloxy)-3-methyl-butan-1-ol (61)

Protection of alcohol **60** as a *p*-methoxybenzyl ether was accomplished using a procedure analogous to that outlined for the conversion of **16** to **17**: NaH (3.45 g, 144 mmol), NaI (2.7 g, 18.0 mmol), THF (200 mL), alcohol **60** (15.4 g, 71.9 mmol) and *p*-methoxybenzyl chloride (6.38 mL, 47. 0 mmol) were used. The crude product was purified by flash column chromatography to afford the *p*-methoxybenzyl ether (23.8 g, 99%) as a colorless oil: $[\alpha]^{25}_D = -34°$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.2 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 5.88 (ddd, *J* = 7.2, 10.0, 17.2 Hz, 1H), 5.07 (d *J* = 17.2 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.61 (AB, *J* = 10.8 Hz, 1H), 4.55 (AB, *J* = 10.8 Hz, 1H), 4.12 (ddd, *J* = 6.4, 7.6, 11.6

Hz, 1H), 4.00 (dd, *J* = 6.0, 7.6 Hz, 1H), 3.78-3.83 (m, 1H), 3.80 (s, 3H), 3.51 (t, *J* = 5.2 Hz, 1H), 2.38-2.48 (m, 1H), 1.55-1.72 (m, 4H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.87-0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 141.3, 130.7, 129.3, 114.4, 113.7, 112.5, 82.4, 76.9, 74.0, 66.5, 55.2, 40.2, 29.7, 29.0, 15.0, 8.2, 8.1; IR (neat) 2972, 1614, 1514, 1248 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{30}O_4Na$ $[M+Na]^+$ calcd 357.2042, found 357.2039.

The hydroboration-oxidation of the *p*-methoxybenzyl ether compound was accomplished using a procedure analogous to that outlined for the conversion of **16** to **17**: the *p*-methoxybenzyl ether (23.8 g, 71.2 mmol), THF (50 mL) and 9-BBN (430 mL of a 0.5 M THF solution, 136 mmol) were used. The crude product was purified by flash column chromatography to afford **61** (24.8 g, 99%) as a colorless oil: $[\alpha]^{25}_D = -21°$ (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.55 (s, 2H), 4.14 (app q, *J* = 6.0 Hz, 1H), 4.07 (dd, *J* = 5.2, 7.6 Hz, 1H), 3.80 (s, 3H), 3.79 (app q, *J* = 7.6 Hz, 1H), 3.69-3.76 (m, 1H), 3.60-3.69 (m, 1H), 3.48 (dd, *J* = 2.8, 6.4 Hz, 1H), 1.98-2.06 (m, 1H), 1.72-1.82 (m, 1H), 1.59-1.70 (m, 4H), 1.50-1.59 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.89 (q, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.5, 129.3, 113.8, 112.5, 83.1, 76.7, 73.6, 67.7, 61.2, 55.3, 36.5, 32.5, 29.8, 29.0, 15.2, 8.2, 8.2; IR (neat) 3418, 2934, 2245, 1614 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{32}O_5Na$ $[M+Na]^+$ calcd 375.2147, found 375.2144.

(*S*)-2,2-Diethyl-4-[(1*R*,2*S*)-1-(4-methoxy-benzyloxy)-2-methyl-pent-4-ynyl]-[1,3]dioxolane (62)

The oxidation of **61** was accomplished using a procedure analogous to that outlined for the conversion of **17** to **18**: alcohol **61** (24.8 g, 70.4 mmol), CH_2Cl_2 (240 mL), DMSO (15.3 mL, 216 mmol), *i*-Pr_2NEt (39 mL, 216 mmol) and SO_3·pyridine (34 g, 216 mmol) were used. The crude product was purified by flash column chromatography to afford the aldehyde (24.4 g, 99%) as a colorless oil: $[\alpha]^{25}_D = -18°$ (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.51 (AB, *J* = 10.8 Hz, 1H), 4.47 (AB, *J* = 11.2 Hz, 1H), 4.30-4.11 (m, 2H), 3.81 (s, 3H), 3.72-3.80 (m, 1H), 3.45 (bdd, *J* = 2.8, 6.8 Hz, 1H), 2.45-2.61 (m, 2H), 2.30-2.45 (m, 1H), 1.55-1.70 (m, 4H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.85-0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 159.2, 130.2, 129.3, 113.7, 112.6, 82.2, 76.5, 73.2, 67.9, 55.2, 47.630.3, 29.7, 28.9, 15.0, 8.1, 8.1; IR (neat) 2972, 1724, 1514, 1249 cm^{-1}; HRMS (ES+) *m/z* for $C_{20}H_{30}O_5Na$ $[M+Na]^+$ calcd 373.1991, found 373.1985.

The Corey-Fuchs homologation of the aldehyde was accomplished using a procedure analogous to that outlined for the conversion of **17** to **18**: the aldehyde (24.4 g, 69 mmol), PPh_3 (30.9 g, 118 mmol), CH_2Cl_2 (235 mL), CBr_4 (23.4 g, 70.6 mmol) and n-BuLi (46 mL of 2.48M hexane solution, 113 mmol) were used were used. Purification of the crude product by flash column chromatography afforded **62** (9.6 g, 59%) as a colorless oil: $[\alpha]^{25}_D = -8.5°$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.59 (AB, *J* = 10.8 Hz, 1H), 4.55 (AB, *J* = 10.8 Hz, 1H), 4.30-4.11 (m, 2H), 3.81 (s, 3H), 3.75-3.82 (m, 1H), 3.70 (bdd, *J* = 3.2, 6.4 Hz, 1H), 2.32 (ddd, *J* = 2.4, 8.0, 16.4 Hz, 1H), 2.20 (ddd, *J* = 2.4, 6.8, 16.4 Hz, 1H), 2.08 (dq, *J* = 4.0, 7.2 Hz, 1H), 2.02 (t, *J* = 2.4 Hz, 1H), 1.58-1.70 (m, 4H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.90 (app dt, *J* = 7.6, 9.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.6, 129.2, 113.7, 112.5, 83.2, 81.0, 76.8, 74.1, 69.6, 67.6, 55.1, 35.2, 29.0, 23.1, 14.2, 8.1; IR (neat) 3294, 2972, 1613, 1515, 1249 cm^{-1}; HRMS (ES+) *m/z* for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ calcd 369.2042, found 369.2033.

(2*R*,3*S*)-2-(4-Methoxy-benzyloxy)-3-methyl-hex-5-ynal (63)

The deprotection of **62** was accomplished using a procedure analogous to that outlined for the conversion of **18** to **19**: alkyne **62** (22.5 g, 64.9 mmol) and a 4:1 mixture of AcOH and water (215 mL). The crude product was purified by flash column chromatography to afford the diol

product (16.9 g, 93%) as a colorless oil: $[\alpha]^{25}_{D}$ = +0.08° (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.61 (AB, *J* = 10.8 Hz, 1H), 4.55 (AB, *J* = 10.8 Hz, 1H), 3.81 (s, 3H), 3.70-3.82 (m, 3H), 3.65 (dd, *J* = 4.0, 6.0 Hz, 1H), 2.19-2.35 (m, 3H), 2.04-2.11 (m, 1H), 2.03 (t, *J* = 2.4 Hz, 1H), 1.94 (b t, *J* = 6.0 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.3, 129.4, 113.8, 83.1, 81.1, 74.3, 71.8, 69.9, 63.8, 55.2, 34.3, 23.3, 14.4; IR (neat) 3401, 3294, 2935, 1614, 1515, 1250, 1074, 1035 cm^{-1}; HRMS (ES+) *m/z* for $C_{16}H_{22}O_4Na$ $[M+Na]^+$ calcd 301.1416, found 301.1418.

Oxidative cleavage of the diol above was accomplished using a procedure analogous to that outlined for the conversion of **18** to **19**: the diol product from the previous step (16.9 g, 60.7 mmol), THF (100 mL), pH 7 buffer (100 mL) and $NaIO_4$ (15.6 g, 72.9 mmol) were used. The product was used without further purification. **63** (12.1 g, 81%) was a colorless oil: $[\alpha]^{25}_{D}$ = +69° (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.6 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 3.94 (bdd, *J* = 1.2, 3.2 Hz, 1H), 3.81 (s, 3H), 2.18-2.38 (m, 3H), 2.00 (t, *J* = 2.4 Hz, 1H), 1.00 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 159.3, 129.6, 129.3, 113.7, 84.5, 82.1, 72.7, 70.2, 55.0, 34.7, 22.2, 14.0; IR (neat) 3291, 2936, 1731, 1514, 1250 cm^{-1}; HRMS (ES+) *m/z* for $C_{15}H_{18}O_3Na$ $[M+Na]^+$ calcd 269.1154, found 269.1146.

(3*R*,4*S*,5*R*,6*S*)-3-(Dimethylphenylsilanyl)-5-(4-methoxy-benzyloxy)-6-methyl-non-1-en-8-yn-4-ol (64)

Hydroxyallylsilane **64** was synthesized using a procedure analogous to that outlined for the conversion of **19** to **21**: aldehyde **63** (11.5 g, 46.7 mmol), 4Å mol. sieves (8.6 g), toluene (80 mL) and (*S*,*S*)-**20** (110 mL of a 1.0M solution in toluene, 110 mmol) were used. The crude product was purified by flash column chromatography to afford **64** (17.7 g, 90%) as a colorless oil: $[\alpha]^{25}_{D}$ = −12° (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.56 (m, 2H), 7.30-7.38 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.98 (dt, *J* = 10.4, 17.2 Hz, 1H), 5.02 (dd, *J* = 2.0, 10.4 Hz, 1H), 4.85 (dd, *J* = 2.0, 17.2 Hz, 1H), 4.59 (AB, *J* = 10.4 Hz, 1H), 4.52 (AB, *J* = 10.4 Hz, 1H), 3.80 (s, 3H), 3.65 (bdt, *J* = 2.4, 8.4 Hz, 1H), 3.52 (bdd, *J* = 2.8, 8.4 Hz, 1H), 2.28-2.31 (m, 1H), 2.20 (ddq, *J* = 2.4, 7.2, 16.8 Hz, 2H), 1.98 (t, *J* = 2.4 Hz, 1H), 1.85-1.92 (m, 1H), 1.82 (bd, *J* = 10.8 Hz, 1H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.38 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 137.8, 134.1, 134.0, 130.6, 129.3, 128.9, 127.6, 114.8, 113.9, 83.8, 83.3, 75.1, 71.6, 69.5, 55.2, 38.3, 34.1, 23.8, 13.4, -3.8, -4.3; IR (neat) 3564, 3303, 2963, 1613, 1514, 1248 cm^{-1}; HRMS (ES+) *m/z* for $C_{26}H_{34}O_3SiNa$ $[M+Na]^+$ calcd 445.2175, found 445.2173.

1-[(1*R*,2*S*,3*R*)-3-(Dimethyl-phenyl-silanyl)-1-((*S*)-1-methyl-but-3-ynyl)-2-triethylsilanyloxy-pent-4-enyloxymethyl]-4-methoxy-benzene (8)

Allylsilane 8 was protected as the triethylsilyl ether using a procedure analogous to that outlined for the conversion of 21 to 7: 64 (0.53 g, 1.3 mmol), DMF (45 mL), imidazole (0.26 g, 3.8 mmol) and triethylsilyl chloride (0.64 mL, 3.8 mmol) were used. The crude product was purified by flash column chromatography to afford **8** (0.60 g, 89%) as a colorless oil: $[\alpha]^{25}_{D}$ = +9.0° (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.54 (m, 2H), 7.29-7.38 (m, 3H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.05 (dt, *J* = 10.4, 17.2 Hz, 1H), 4.98 (dd, *J* = 2.0, 10.0 Hz, 1H), 4.82 (dd, *J* = 2.0, 17.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.02 (dd, *J* = 2.0, 6.0 Hz, 1H), 3.81 (s, 3H), 3.20 (t, *J* = 5.2 Hz, 1H), 2.28 (dq, *J* = 2.4, 8.8 Hz, 1H), 2.18 (dd, *J* = 1.6, 10.4 Hz, 1H), 1.92-2.10 (m, 2H), 1.91 (t, *J* = 2.4 Hz, 1H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.88 (t, *J* = 8.0 Hz, 9H), 0.46-0.56 (m, 6H), 0.35 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 138.0, 135.7, 134.2, 131.1, 128.9, 128.8, 127.6, 114.3, 113.5, 84.5, 83.8, 73.1, 72.6, 69.1, 55.2, 38.2, 33.8, 23.8, 15.3, 7.1, 5.5, -3.1, -4.1; IR (neat) 3310, 2956, 1614, 1514, 1248, 1112 cm^{-1}; HRMS (ES+) *m/z* for $C_{32}H_{48}O_3Si_2Na$ $[M+Na]^+$ calcd 559.3040, found 559.3030.

(4*R*,5*R*)-4-((*E*)-4-{(2*S*,4*S*,5*R*)-4-(Dimethyl-phenyl-silanyl)-5-[(1*S*,2*R*,3*S*)-2-(4-methoxy-benzyloxy)-3-methyl-1-triethylsilanyloxy-hex-5-ynyl]-tetrahydro-furan-2-yl}-but-1-enyl)-2,2-dimethyl-5-vinyl-[1,3]dioxolane (65)

Tetrahydrofuran 65 was synthesized using a procedure analogous to that outlined for **24**: aldehyde **5** (0.079 g, 0.37 mmol), allylsilane **8** (0.60 g, 1.12 mmol), activated 4 Å molecular sieves (0.15 g), dichloromethane (0.75 mL) and $BF_3{\cdot}OEt_2$ (47 μL, 0.37 mmol) were used. Purification of the crude product by flash column chromatography afforded **65** (0.171 g, 61%; 0.43 g of allylsilane **8** was recovered) as a colorless oil: $[\alpha]^{25}_D$ = +19° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.50 (m, 2H), 7.36-7.35 (m, 3H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.72-5.84 (m, 2H), 5.42 (bdd, *J* = 6.8, 15.2 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.00-4.08 (m, 2H), 3.96 (d, *J* = 8.4 Hz, 1H), 3.78 (s, 3H), 3.66-3.75 (m, 1H), 3.64 (d, *J* = 6.8 Hz, 1H), 3.46 (bdd, *J* = 4.4, 6.4 Hz, 1H), 2.32-2.42 (m, 1H), 2.21-2.25 (m, 4H), 1.94 (s, 1H), 1.79-1.89 (m, 1H), 1.56-1.74 (m, 3H), 1.36-1.48 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 0.90-1.00 (m, 12H), 0.54-0.64 (m, 6H), 0.35 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 137.7, 136.4, 134.3, 133.9, 131.3, 129.1, 128.6, 127.8, 125.6, 118.3, 113.5, 108.7, 84.2, 82.7, 82.2, 82.1, 81.2, 78.0, 74.0, 73.7, 69.1, 55.1, 35.2, 34.7, 34.5, 29.2, 27.0, 26.9, 25.4, 23.5, 14.9, 7.1, 5.3, -3.7, -4.4; IR (neat) 3308, 2955, 1614, 1514, 1248 cm^{-1}; HRMS (ES+) *m/z* for $C_{44}H_{66}O_6Si_2Na$ $[M+Na]^+$ calcd 769.4296, found 769.4307.

(1*R*,2*R*,3*S*)-1-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-2-(4-methoxy-benzyloxy)-3-methyl-hex-5-yn-1-ol (66)

The protiodesilylation of 65 was accomplished using a procedure analogous to that outlined for the conversion of **24** to **25**: [3+2] adduct **65** (1.26 g, 1.69 mmol), DMF (1.7 mL), TBAF•$3H_2O$ (4.66 g, 14.8 mmol, added portionwise) were used. The crude product was purified by flash column chromatography to afford **66** (0.68 g, 81%) as a colorless oil: $[\alpha]^{25}_D$ =-4.1° (*c* 0.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.73-5.83 (m, 2H), 5.42 (bdd, *J* = 6.0, 15.2 Hz, 1H), 5.33 (d, *J* = 16.8 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.60 (app q, *J* = 10.8 Hz, 2H), 4.01-4.07 (m, 2H), 3.90 (bdt, *J* = 4.8, 5.2 Hz, 1H), 3.84 (bt, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 3.46-3.57 (m, 2H), 2.52-2.57 (m, 1H), 2.30 (ddq, *J* = 2.8, 7.2, 16.8 Hz, 2H), 2.08-2.20 (m, 3H), 1.99 (t, *J* = 2.8 Hz, 1H), 1.88-1.96 (m, 1H), 1.64-1.86 (m, 3H), 1.46-1.62 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 136.0, 134.3, 130.6, 129.5, 126.0, 118.5, 113.8, 108.8, 83.2, 82.2, 82.2, 81.0, 80.2, 79.3, 73.7, 73.7, 69.5, 55.2, 35.1, 35.0, 31.1, 29.1, 27.7, 27.1, 27.0, 22.8, 15.0; IR (neat) 3523, 2985, 1613, 1515, 1248, 1053 cm^{-1}; HRMS (ES+) *m/z* for $C_{30}H_{42}O_6Na$ $[M+Na]^+$ calcd 521.2879, found 521.2879.

(1*S*,2*R*,3*S*)-1-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-3-methyl-1-triethylsilanyloxy-hex-5-yn-2-ol (67)

Protection of 66 as the triethylsilyl ether was accomplished using a procedure analogous to that outlined for the conversion of 24 to 25: alcohol 66 (0.40 g, 0.80 mmol), triethylamine (0.22 mL, 1.6 mmol), dichloromethane (3 mL) and triethylsilyl trifluoromethanesulfonate (0.22 mL, 0.96 mmol) were used.

Deprotection of the *p*-methoxybenzyl ether from the above intermediate was accomplished using a procedure analogous to that outlined for the conversion of 24 to 25: dichloromethane (10 mL), pH 7 buffer (1 mL) and DDQ (0.37 g, 1.6 mmol) were used. Purification of the crude product by flash column chromatography afforded **67** (0.34 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ = +18° (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.85 (m, 2H), 5.44 (bddd, *J* = 1.2, 6.0, 15.6 Hz, 1H), 5.34 (d, *J* = 17.6 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.02-4.10 (m, 2H), 3.81-3.88 (m, 1H), 3.74-3.81 (m, 1H), 3.67 (dd, *J* = 2.0, 6.8 Hz, 1H), 3.42 (ddd, *J* = 2.0, 7.2, 9.2 Hz, 1H), 2.46 (d, *J* = 8.8 Hz, 1H), 2.07-2.32 (m, 4H), 1.96 (t, *J* = 2.4 Hz, 1H), 1.76-1.98

(m, 3H), 1.50-1.71 (m, 3H), 1.42-1.50 (m, 1H), 1.44 (s, 3H), 1.44 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 9H), 0.59-0.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 134.3, 125.9, 118.3, 108.7, 82.2, 82.2, 82.1, 81.1, 78.6, 75.1, 73.3, 69.8, 35.5, 35.1, 30.8, 29.1, 27.2, 27.0, 26.9, 22.7, 15.0, 6.9, 5.3; IR (neat) 3535, 3311, 2955, 1239, 1056, 741 cm^{-1}; HRMS (ES +) *m/z* for $C_{28}H_{48}O_5SiNa$ $[M+Na]^+$ calcd 515.3169, found 515.3160.

2-*epi*-19-*epi*-Amphidinolide E (4) series

Tricarbonyl[(*E*)-(2*R*,3*S*)-2-Methyl-hexa-3,5-dienoic acid (1*R*,2*S*)-1-((*R*)-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-triethylsilanyloxy-methyl)-2-methyl-pent-4-ynyl ester]iron (70)

The esterification of alcohol 67 was accomplished using a procedure analogous to that outlined for 39: alcohol 67 (0.33 g, 0.67 mmol), acid **10** (0.22 g, 0.80 mmol), triethylamine (0.22 mL, 1.6 mmol), DMAP (0.082 g, 0.67 mmol), THF (1.4 mL) and 2,4,6-trichlorobenzoyl chloride (125 μL, 0.80 mmol) were used. Purification of the crude product by flash column chromatography afforded **70** (0.418 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ = −2.6° (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75-5.83 (m, 2H), 5.41-5.47 (m, 1H), 5.35-5.40 (m, 1H), 5.34 (app d, *J* = 23.6 Hz, 1H), 5.25-5.30 (m, 1H), 5.23 (app d, *J* = 12.0 Hz, 1H), 4.89 (dd, *J* = 2.4, 7.6 Hz, 1H), 4.03-4.08 (m, 2H), 3.70-3.79 (m, 1H), 3.71 (dd, *J* = 3.2, 7.2 Hz, 1H), 3.59-3.65 (m, 1H), 2.05-2.37 (m, 6H), 1.98 (t, *J* = 2.0 Hz, 1H), 1.85-1.95 (m, 1H), 1.75-1.85 (m, 2H), 1.60-1.70 (m, 1H), 1.50-1.60 (m, 2H), 1.40-1.50 (m, 1H), 1.44 (s, 3H), 1.44 (s, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.93-0.99 (m, 1H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.59-0.73 (m, 6H), 0.35 (bdd, *J* = 2.0, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 173.6, 136.1, 134.3, 125.9, 118.4, 108.8, 87.1, 82.2, 82.2, 81.8, 80.4, 78.6, 77.2, 76.9, 74.9, 70.1, 64.0, 44.6, 40.4, 35.1, 33.0, 30.9, 29.2, 27.5, 27.0, 27.0, 22.7, 19.3, 15.6, 7.0, 5.3; IR (neat) 3312, 2877, 2050, 1982, 1732, 1380, 1239 cm^{-1}; HRMS (ES+) *m/z* for $C_{38}H_{56}FeO_9SiNa$ $[M+Na]^+$ calcd 763.2941, found 763.2958.

(4*E*,11*E*,13*E*)-(1*S*,6*R*,10*R*,15*S*,18*R*,19*R*,20*S*)-18-((*S*)-3-Iodo-1-methyl-but-3-enyl)-8,8,15-trimethyl-19-triethylsilanyloxy-7,9,17,23-tetraoxa-tricyclo[18.2.1.$0^{6,10}$]tricosa-4,11,13-trien-16-one (71)

The oxidative decomplexation of 70 was accomplished using a procedure analogous to that outlined for the conversion of 39 to 40: ester 70 (173 mg, 0.234 mmol), acetone (3 mL) and cerium ammonium nitrate (CAN) (0.28 g, 0.51 mmol) were used. The crude product was purified by flash column chromatography to afford the polyene product (135 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ = +16° (*c* 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dt, *J* = 10.4, 16.8, 1H), 6.14 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.71-5.84 (m, 3H), 5.39-5.47 (m, 1H), 5.32 (d, *J* = 17.6 Hz, 1H), 5.22 (d, *J* = 11.6 Hz, 1H), 5.16 (d, *J* = 16.4, 1H), 5.05 (d, *J* = 10.0 Hz, 1H), 4.88 (dd, *J* = 2.8, 7.6 Hz, 1H), 4.01-4.07 (m, 2H), 3.61-3.77 (m, 3H), 3.20 (quint., *J* = 7.2 Hz, 1H), 2.26-2.37 (m, 1H), 2.04-2.26 (m, 4H), 1.96 (t, *J* = 2.0 Hz, 1H), 1.75-1.93 (m, 2H), 1.49-1.70 (m, 3H), 1.40-1.46 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.29 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 5.6 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.56-0.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 136.4, 136.2, 134.3, 132.6, 132.2, 125.9, 118.5, 117.0, 108.8, 82.2, 82.2, 82.0, 80.3, 78.6, 76.8, 74.9, 70.0, 43.1, 35.1, 33.1, 30.9, 29.2, 27.5, 27.0, 27.0, 22.7, 17.1, 15.4, 7.0, 5.3; IR (neat) 3311, 2954, 2877, 1733, 1456, 1240, 1171 cm^{-1}; HRMS (ES+) *m/z* for $C_{35}H_{56}O_6SiNa$ $[M+Na]^+$ calcd 623.3744, found 623.3751.

The ring closing metathesis of the polyene intermediate was accomplished by using a procedure analogous to that outlined for the conversion of **39** of **40**: polyene from the preceding step (40 mg, 0.066 mmol), dichloromethane (66 mL) and Grubbs' first generation catalyst (11 mg, 0.013 mmol) were used. The crude product was purified by flash column chromatography to afford the macrocycle product (22 mg, 58%) as a colorless oil. In addition, an inseparable mixture of

products thought to arrive by enyne metathesis (3.8 mg, 10%) was also isolated. Spectroscopic data for macrocycle product: $[\alpha]^{25}_{D} = -48°$ (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15-6.28 (m, 2H), 5.94 (dd, *J* = 4.8, 14.4 Hz, 1H), 5.72 (ddd, *J* = 3.6, 9.6, 15.2 Hz, 1H), 5.57 (dd, *J* = 8.8, 14.4 Hz, 1H), 5.34 (dd, *J* = 8.4, 15.2 Hz, 1H), 4.74 (d, *J* = 8.4 Hz, 1H), 3.99-4.08 (m, 2H), 3.72 (d, *J* = 8.4 Hz, 1H), 3.29-3.38 (m, 1H), 3.18-3.30 (m, 2H), 2.18-2.36 (m, 4H), 1.80-2.20 (m, 2H), 1.98 (bs, 1H), 1.64-1.74 (m, 1H), 1.40-1.57 (m, 2H), 1.43 (s, 6H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.15-1.32 (m, 2H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.53-0.70 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 138.1, 136.0, 134.6, 128.8, 127.4, 125.9, 109.0, 83.1, 82.2, 81.5, 79.8, 77.8, 77.4, 77.2, 75.0, 70.2, 43.3, 32.2, 32.1, 29.6, 28.5, 27.2, 27.1, 22.1, 15.8, 12.0, 7.1, 5.6; IR (neat) 3309, 2934, 2874, 1727, 1458, 1378, 1238, 1052 cm^{-1}; HRMS (ES+) *m/z* for $C_{33}H_{52}O_6SiNa$ $[M+Na]^+$ calcd 595.3431, found 595.3439.

The stannylalumination-protonolysis of the alkyne from the preceding step was accomplished using a procedure analogous to that outlined for the conversion of **40** to **41**: macrocycle alkyne (51 mg, 0.089 mmol), THF (1.5 mL), Bu_3Sn-$AlEt_2$ (1.3 mL of the 0.42M solution, 0.53 mmol) and CuCN (2 mg, 0.024 mmol) were used. Purification of the crude product by flash column chromatography afforded the vinylstannane product (40 mg, 52%) as a colorless oil: $[\alpha]^{25}_{D} = -138°$ (*c* 0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15-6.29 (m, 2H), 5.95 (dd, *J* = 4.8, 14.8 Hz, 1H), 5.67-5.78 (m, 2H), 5.57 (dd, *J* = 8.4, 14.0 Hz, 1H), 5.35 (dd, *J* = 8.0, 15.2 Hz, 1H), 5.20 (app t, $^3J_{Sn\text{-}H}$ = 34.0 Hz, 1H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.04 (app quint., *J* = 9.6 Hz, 2H), 3.68 (d, *J* = 8.4 Hz, 1H), 3.20-3.38 (m, 3H), 2.48 (bd, *J* = 18.0 Hz, 1H), 2.26-2.35 (m, 1H), 2.09-2.19 (m, 1H), 1.84-2.06 (m, 3H), 1.64-1.74 (m, 1H), 1.41-1.57 (m, 8H), 1.44 (s, 6H), 1.24-1.36 (m, 11H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.85-0.92 (m, 15H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.58-0.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 152.9, 138.2, 136.0, 134.7, 128.8, 127.3, 126.7, 125.9, 109.0, 83.1, 82.2, 80.1, 78.6, 76.0, 44.2, 43.5, 33.2, 32.3, 29.7, 29.1, 28.5, 27.4, 27.2, 27.1, 15.5, 13.7, 12.0, 10.7, 10.5, 9.5, 7.1, 5.7; IR (neat) 2930, 1727, 1239, 1052 cm^{-1}; HRMS (ES+) *m/z* for $C_{45}H_{80}O_6SiSnNa$ $[M+Na]^+$ calcd 887.4644, found 887.4681.

Iododestannylation of the vinylstannane intermediate was accomplished using a procedure analogous to that outlined for the conversion of **40** to **41**: vinylstannane from above (11 mg, 0.013 mmol), dichloromethane (1 mL) and NIS (3.2 mg, 0.014 mmol) were used. The crude product was purified by flash column chromatography to afford **71** (9 mg, 98%) as a colorless oil: $[\alpha]^{25}_{D} = -46°$ (*c* 0.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15-6.29 (m, 2H), 6.09 (s, 1H), 5.89-5.98 (m, 1H), 5.76 (s, 1H), 5.68-5.76 (m, 1H), 5.58 (dd, *J* = 8.8, 12.4 Hz, 1H), 5.34 (dd, *J* = 8.0, 14.8 Hz, 1H), 4.59 (d, *J* = 7.2 Hz, 1H), 3.98-4.90 (m, 2H), 3.66 (d, *J* = 8.4 Hz, 1H), 3.20-3.37 (m, 3H), 2.61 (bd, *J* = 13.6 Hz, 1H), 2.26-2.38 (m, 2H), 2.08-2.17 (m, 1H), 1.84-2.02 (m, 2H), 1.62-1.74 (m, 1H), 1.40-1.54 (m, 1H), 1.43 (s, 6H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.12-1.30 (m, 1H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.61-0.69 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 138.2, 136.0, 134.3, 128.9, 127.5, 127.4, 126.0, 110.6, 109.0, 83.1, 82.2, 79.9, 77.6, 77.4, 75.9, 48.5, 43.4, 33.3, 32.2, 29.7, 29.6, 28.5, 27.2, 27.1, 14.7, 12.1, 7.2, 5.6; IR (neat) 2934, 1726, 1238, 1052 cm^{-1}; HRMS (ES+) *m/z* for $C_{33}H_{53}IO_6SiNa$ $[M+Na]^+$ calcd 723.2554, found 723.2567.

2-*epi*-19-*epi*-amphidinolide E (4)

Deprotection of **71** was accomplished using a procedure analogous to that outlined for the conversion of **41** to **2**: vinyl iodide **71** (26 mg, 0.037 mmol) and AcOH, THF and water (4/1/1 ratio) (1 mL) were used. Analysis of the crude product by ^{1}H NMR indicated a 2:1 mixture of the desired C(18) and undesired C(17) lactones.

Stille coupling of the crude mixure of lactones from above was accomplished using a procedure analogous to that outlined for the conversion of **41** to **2**: CuCl (18 mg, 0.18 mmol), THF (0.5 mL), vinylstannane **6** (61 mg, 0.17 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were used. The crude product was purified by flash column chromatography using 10% methanol/chloroform

to afford material that was still contaminated with an organotin impurity. The stannane impurity was removed by HPLC purification with 100% ethyl acetate eluent on a normal phase, Varian Dynamax Microsorb 60-8 Si, 250 × 21.4 mm column. The retention time for 2-*epi*-19-*epi*-amphidinolide E was 7.6 min. The flow rate was 18 mL/min. 2-*epi*-19-*epi*-mphidinolide E was detected using UV absorption (λ = 254 nm and 280 nm) and RI detection. Using the above conditions 6 mg (32% from **71**) of pure 2-*epi*-19-*epi*-amphidinolide E was isolated: $[\alpha]^{25}_{D}$ = −51° (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15-6.25 (m, 2H), 6.05 (d, *J* = 16.0 Hz, 1H), 5.94-6.01 (m, 1H), 5.85 (dt, *J* = 7.2, 15.6 Hz, 1H), 5.55-5.70 (m, 2H), 5.30 (dd, *J* = 7.6, 15.2 Hz, 1H), 4.98 (s, 1H), 4.88 (s, 1H), 4.74 (s, 1H), 4.70 (s, 1H), 4.69 (d, *J* = 10.4 Hz, 1H), 3.90-4.01 (m, 2H), 3.71-3.77 (m, 1H), 3.46-3.54 (m, 1H), 3.38-3.46 (m, 1H), 3.29-3.38 (m, 1H), 2.78 (bd, *J* = 6.4 Hz, 2H), 2.60 (dd, *J* = 3.6, 12.8 Hz, 1H), 2.22-2.41 (m, 5H), 1.73-1.96 (m, 4H), 1.72 (s, 3H), 1.36-1.70 (m, 4H), 1.34 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 144.8, 144.0, 134.8, 134.2, 134.1, 133.1, 131.2, 129.7, 129.6, 128.4, 116.2, 110.9, 79.9, 78.2, 77.3, 76.5, 73.3, 43.2, 41.5, 36.1, 32.8, 32.3, 30.2, 29.1, 27.4, 22.7, 15.7, 13.4; IR (neat) 3401, 2931, 1724, 1238, 1047, 991 cm^{-1}; HRMS (ES+) *m/z* for $C_{30}H_{44}O_6Na$ $[M+Na]^+$ calcd 523.3036, found 523.3030.

Amphidinolide E (1) series

tert-Butyl-dimethyl-((*E*)-(*R*)-2-methyl-hexa-3,5-dienyloxy)-silane (75)

To a −78 °C solution of **45**[49] (4.19 g, 20.7 mmol) and γ-(TMS)-allyltributylstannane (11.7 g, 29.0 mmol) in CH_2Cl_2 (21 mL) was added $BF_3{\cdot}OEt_2$ (2.89 mL, 22.8 mmol). The reaction was stirred for 30 min, then quenched at −78 °C with sat. aq. $NaHCO_3$ (60 mL) and extracted with CH_2Cl_2 (40 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residual was dissolved in THF (20 mL) and treated with KO*t*-Bu (2.0 g, 18 mmol). The reaction was stirred for 3 h at room temperature and then poured into a separatory funnel containing Et_2O (100 mL) and sat. aq. $NaHCO_3$ (200 mL). The aqueous layer was extracted with Et_2O (50 mL × 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by flash column chromatography afforded **75** (2.75 g, 59%) as a colorless oil: $[\alpha]^{25}_{D}$ = +11° (*c* 4.8, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.31 (dt, *J* = 10.4, 16.8 Hz, 1H), 6.08 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.64 (dd, *J* = 7.2, 15.2 Hz, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 3.51 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.41 (dd, *J* = 6.8, 9.6 Hz, 1H), 2.37 (sept., *J* = 6.8 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ^3 137.6, 137.4, 130.5, 115.2, 67.9, 39.3, 25.9, 18.3, 16.4, −5.3, −5.4; IR (neat) 2957, 1799, 1472, 1256, 1115, 1088, 837 cm^{-1}; HRMS (EI+) *m/z* for $C_9H_{17}OSi$ $[M–C_4H_9]^+$ calcd 169.1049, found 169.1044.

Tricarbonyl[(*E*)-(2*S*,3*R*)-2-Methyl-hexa-3,5-dienoic acid (1*R*,2*R*)-1-((*R*)-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-triethylsilanyloxy-methyl)-2-methyl-pent-4-ynyl ester]iron (76)

The esterification of alcohol 25 to acid 9 was accomplished using a procedure analogous to that outlined for 39: alcohol 25 (120 mg, 0.244 mmol), acid **9** (105 mg, 0.390 mmol), triethylamine (0.12 mL, 0.854 mmol), DMAP (30 mg, 0.244 mmol), THF (0.5 mL) and 2,4,6-trichlorobenzoyl chloride (61 μL, 0.390 mmol) were used. Purification of the crude product by flash column chromatography afforded **76** (179 mg, 99%) as a colorless oil: $[\alpha]^{25}_{D}$ = +13° (*c* 0.18, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.74-5.81 (m, 2H), 5.43 (app dd, *J* = 4.8, 8.4 Hz, 2H), 5.33 (d, *J* = 16.8 Hz, 1H), 5.21-5.26 (m, 1H), 5.22 (d, *J* = 11.6 Hz, 1H), 4.69 (dd, *J* = 1.2, 9.2 Hz, 1H), 4.04 (app q, *J* = 6.8 Hz, 2H), 3.72 (quint., *J* = 5.6, 1H), 3.67 (dd, *J* = 1.6, 7.6 Hz, 1H), 3.60 (app q, *J* = 8.0 Hz, 1H), 1.99-2.32 (m, 7H), 1.94 (t, *J* = 2.8 Hz, 1H), 1.73-1.88 (m, 3H), 1.50-1.66 (m, 2H), 1.38-1.48 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.97 (app d, *J* = 8.0 Hz, 1H), 0.59-0.76

(m, 6H), 0.32 (bdd, *J* = 1.6, 9.2 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 211.2, 173.7, 136.1, 134.3, 126.0, 118.5, 108.9, 87.5, 82.2, 82.2, 82.2, 80.7, 78.5, 77.4, 77.2, 75.4, 69.7, 63.9, 44.5, 40.4, 35.2, 33.3, 30.9, 29.2, 27.8, 27.1, 26.9, 22.3, 19.2, 16.1, 7.1, 5.4; IR (neat) 3310, 2049, 1978, 1732, 1238, 1170 cm^{-1}; HRMS (ES+) *m/z* for $C_{38}H_{56}FeO_9SiNa$ $[M+Na]^+$ calcd 763.2941, found 763.2944.

(*E*)-(*R*)-2-Methyl-hexa-3,5-dienoic acid (1*R*,2*R*)-1-((*R*)-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-triethylsilanyloxy-methyl)-2-methyl-pent-4-ynyl ester (72)

The oxidative decomplexation of 76 was accomplished using a procedure analogous to that outlined for the conversion of 39 to 40: 76 (45 mg, 0.061 mmol), acetone (1 mL) and cerium ammonium nitrate (CAN) (67 mg, 0.122 mmol) were used. The crude product was purified by flash column chromatography to afford **72** (35 mg, 95%) as a colorless oil: $[\alpha]^{25}_D = -1.0°$ (*c* 0.10, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.29 (dt, *J* = 10.0, 16.8, 1H), 6.15 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.72-5.82 (m, 3H), 5.42 (bdd, *J* = 1.6, 6.0, 15.6 Hz, 1H), 5.32 (d, *J* = 16.4 Hz, 1H), 5.22 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.17 (d, *J* = 17.6, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.70 (dd, *J* = 2.0, 8.8 Hz, 1H), 4.04 (app q, *J* = 7.2 Hz, 2H), 3.71 (quint., *J* = 5.6 Hz, 1H), 3.67 (dd, *J* = 2.0, 7.2 Hz, 1H), 3.59 (q, *J* = 6.4 Hz, 1H), 3.21 (quint., *J* = 7.2 Hz, 1H), 1.98-2.36 (m, 5H), 1.94 (t, *J* = 2.4 Hz, 1H), 1.74-1.88 (m, 2H), 1.57-1.66 (m, 1H), 1.46-1.56 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.36-1.45 (m, 2H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 6.8 Hz, 9H), 0.57-0.72 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.7, 136.3, 136.2, 134.3, 132.5, 132.3, 125.8, 118.5, 117.0, 108.8, 82.4, 82.2, 82.2, 80.4, 78.4, 77.4, 75.3, 69.6, 42.8, 35.2, 33.3, 30.9, 29.2, 27.0, 26.9, 22.2, 17.0, 16.1, 7.0, 5.3; IR (neat) 3310, 2953, 2876, 1733, 1378, 1239 cm^{-1}; HRMS (ES+) *m/z* for $C_{35}H_{56}O_6SiNa$ $[M+Na]^+$ calcd 623.3744, found 623.3748.

(4*E*,11*E*,13*E*)-(1*S*,6*R*,10*R*,15*R*,18*R*,19*R*,20*S*)-18-((*R*)-3-Iodo-1-methyl-but-3-enyl)-8,8,15-trimethyl-19-triethylsilanyloxy-7,9,17,23-tetraoxa-tricyclo[18.2.1.$0^{6,10}$]tricosa-4,11,13-trien-16-one (77)

The ring closing metathesis of 72 was accomplished using a procedure analogous to that outlined for the conversion of 39 to 40: polyene 72 (63 mg, 0.105 mmol), dichloromethane (105 mL) and Grubbs' first generation catalyst (17 mg, 0.021 mmol) were used. The crude product was purified by flash column chromatography to afford the macrocycle product (44 mg, 73%) as a colorless oil. In addition, an inseparable mixture of products thought to arrive by enyne metathesis (4 mg, 10%) was also isolated. Spectroscopic data for the macrocycle product: $[\alpha]^{25}_D = -34°$ (*c* 0.21, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.15-6.26 (m, 2H), 5.72 (ddd, *J* = 3.6, 9.6, 15.2 Hz, 1H), 5.49-5.57 (m, 2H), 5.33 (app dd, *J* = 8.4, 15.6 Hz, 1H), 4.55 (app dd, *J* = 1.6, 9.6 Hz, 1H), 4.02 (app dt, *J* = 8.4, 26.0 Hz, 2H), 3.71 (app dd, *J* = 1.6, 8.4 Hz, 1H), 3.20-3.35 (m, 3H), 2.19-2.36 (m, 3H), 1.82-2.03 (m, 3H), 1.95 (t, *J* = 2.8 Hz, 1H), 1.62-1.70 (m, 1H), 1.50-1.59 (m, 1H), 1.38-1.49 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.15-1.28 (m, 2H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 9H), 0.57-0.73 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.2, 138.4, 135.5, 131.3, 127.6, 125.7, 109.0, 83.0, 82.9, 82.3, 79.9, 78.5, 77.2, 75.1, 69.3, 44.2, 33.2, 32.0, 29.6, 28.6, 27.2, 27.1, 27.0, 22.5, 16.9, 15.6, 7.1, 5.6; IR (neat) 3310, 2950, 2874, 1732, 1378, 1237, 1170, 1053 cm^{-1}; HRMS (ES+) *m/z* for $C_{33}H_{52}O_6SiNa$ $[M+Na]^+$ calcd 595.3431, found 595.3442.

Stannylalumination-protonolysis of the macrocycle alkyne was accomplished using a procedure analogous to that outlined for the conversion of **40** to **41**: macrocycle alkyne from the preceding step **17** (44 mg, 0.077 mmol), THF (1 mL), Bu_3Sn-$AlEt_2$ (1.1 mL of the 0.41M solution, 0.45 mmol) and CuCN (2 mg, 0.022 mmol) were used. Purification of the crude product by flash column chromatography afforded the vinylstannane (38 mg, 58%) as a colorless oil: $[\alpha]^{25}_D = -34.5°$ (*c* 0.11, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.15-6.26 (m,

2H), 5.72 (app ddd, *J* = 3.6, 9.6, 15.2 Hz, 1H), 5.63 (app t, $^3J_{Sn-H}$ = 70 Hz, 1H), 5.50-5.90 (m, 2H), 5.34 (dd, *J* = 8.8,15.2 Hz, 1H), 5.14 (dt, J = 2.4 Hz, $^3J_{Sn-H}$ = 31.6 Hz, 1H), 4.50 (d, *J* = 10.0 Hz, 1H), 4.02 (app dt, *J* = 8.8, 24.0 Hz, 2H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.15-3.35 (m, 3H), 2.33 (d, *J* = 13.2 Hz, 2H), 1.82-2.06 (m, 4H), 1.60-1.70 (m, 1H), 1.40-1.57 (m, 8H), 1.44 (s, 3H), 1.43 (s, 3H), 1.25-1.36 (m, 7H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.18-1.24 (m, 2H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.93-0.99 (m, 1H), 0.85-0.93 (m, 14H), 0.81 (d, *J* = 6.4 Hz, 3H), 0.55-0.72 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.2, 154.1, 138.5, 136.0, 135.8, 131.1, 127.5, 126.7, 125.7, 109.0, 83.1, 82.4, 80.1, 79.6, 77.2, 75.0, 45.4, 44.4, 33.0, 32.1, 29.7, 29.2, 29.1, 28.5, 27.4, 27.2, 27.1, 16.9, 14.8, 13.7, 9.6, 7.2, 5.7; IR (neat) 2954, 2931, 2873, 1732, 1237, 1170, 1053 cm^{-1}; HRMS (ES+) *m/z* for $C_{45}H_{80}O_6SiSnNa$ $[M+Na]^+$ calcd 887.4644, found 887.4655.

Iododestannylation of the vinylstannane intermediate was accomplished using a procedure analogous to that outlined for the conversion of **40** to **41**: vinylstannane from the preceding step (121 mg, 0.140 mmol), dichloromethane (2 mL) and NIS (38 mg, 0.17 mmol) were used. The crude product was purified by flash column chromatography to afford **77** (94 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ = −63° (*c* 0.13, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.15-6.28 (m, 2H), 6.04 (s, 1H), 5.73 (s, 1H), 5.72 (ddd, *J* = 4.0, 10.4, 14.8 Hz, 1H), 5.53 (app dt, *J* = 9.2, 14.4 Hz, 2H), 5.33 (dd, *J* = 8.8, 15.2 Hz, 1H), 4.56 (d, *J* = 10.0 Hz, 1H), 4.02 (app dt, *J* = 8.8, 28.4 Hz, 2H), 3.73 (d, *J* = 8.8 Hz, 1H), 3.20-3.37 (m, 3H), 2.28-2.48 (m, 3H), 2.00 (dd, *J* = 10.0, 13.6 Hz, 3H), 1.82-1.95 (m, 2H), 1.62-1.70 (m, 1H), 1.49-1.58 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.31-1.46 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.16-1.20 (m, 1H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.56-0.75 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.4, 138.3, 135.9, 135.5, 131.3, 127.7, 127.1, 125.7, 111.4, 109.0, 83.1, 82.3, 80.0, 78.6, 77.2, 75.0, 48.0, 44.1, 32.7, 32.0, 29.5, 28.5, 27.2, 27.0, 16.9, 14.5, 7.2, 5.7; IR (neat) 2950, 2874, 1731, 1378, 1237, 1170, 1053 cm^{-1}; HRMS (ES+) *m/z* for $C_{33}H_{53}IO_6SiNa$ $[M+Na]^+$ calcd 723.2554, found 723.2559.

Amphidinolide E (1)

Deprotection of **77** was accomplished using a procedure analogous to that outlined for the conversion of **41** to **2**: vinyl iodide **77** (15 mg, 0.021 mmol) and AcOH, THF and water (4/1/1) (0.5 mL) were used. The crude product was purified by flash column chromatography to afford only the C18 lactone (9 mg, 77%) as a colorless oil: $[\alpha]^{25}_D$ = −14.2° (*c* 0.12, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.10-6.28 (m, 2H), 6.05 (s, 1H), 5.74 (s, 1H), 5.50-5.69 (m, 3H), 5.26 (dd, *J* = 8.0, 15.2 Hz, 1H), 4.68 (d, *J* = 9.2 Hz, 1H), 3.91 (app dt, *J* = 8.8, 28.8 Hz, 2H), 3.68-3.74 (m, 1H), 3.55 (app q, *J* = 7.6 Hz, 1H), 3.36-3.44 (m, 1H), 3.22-3.31 (m, 1H), 3.35-2.57 (m, 4H), 2.23-2.31 (m, 1H), 2.05 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.72-1.93 (m, 3H), 1.29-1.62 (m, 5H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.4, 135.0, 134.9, 134.1, 131.5, 129.5, 127.3, 110.7, 79.8, 78.1, 77.6, 77.2, 77.1, 76.6, 73.3, 48.4, 44.0, 33.2, 32.5, 29.9, 29.0, 27.1, 17.5, 14.7; IR (neat) 3428, 2932, 2873, 1729, 1167, 990 cm^{-1}; HRMS (ES+) *m/z* for $C_{24}H_{35}IO_6Na$ $[M+Na]^+$ calcd 569.1376, found 569.1369.

Stille coupling of the C18 lactone from above was accomplished using a procedure analogous to that outlined for the conversion of **41** to **2**: vinyl iodide lactone from the preceding step (20 mg, 0.037 mmol), CuCl (20 mg, 0.201 mmol), THF (0.5 mL), vinylstannane **6** (68 mg, 0.183 mmol) and $Pd(PPh_3)_4$ (8.5 mg, 0.00732 mmol) were used. The crude product was purified by flash column chromatography using 10% methanol/chloroform to afford material that was still contaminated with an organotin impurity. The stannane impurity was removed by HPLC purification with 100% ethyl acetate eluent on a normal phase, Varian Dynamax Microsorb 60-8 Si, 250 × 21.4 mm column. The retention time for amphidinolide E was 9.5 min. The flow rate was 18 mL/min. Amphidinolide E was detected using UV absorption (λ = 254 nm and 280 nm) and RI detection. Using the above conditions 10.6 mg (59%) of pure synthetic amphidinolide E was isolated: $[\alpha]^{25}_D$ = −86° (*c* 0.08, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ

6.10-6.28 (m, 2H) (H4 and H5), 6.05 (d, *J* = 15.2 Hz, 1H) (H22), 5.58-5.75 (m, 3H) (H3, H10, H23), 5.53 (dd, J = 8.8, 14.4, 1H) (H6), 5.27 (dd, *J* = 7.6, 14.4 Hz, 1H) (H9), 4.98 (s, 1H) (H29), 4.87 (s, 1H) (H29), 4.75 (s, 1H) (H26), 4.71 (s, 1H) (H26), 4.66 (d, *J* = 9.2 Hz, 1H) (H18), 3.95 (t, *J* = 8.4 Hz, 1H) (H8), 3.89 (t, *J* = 8.8 Hz, 1H) (H7), 3.68-3.74 (m, 1H) (H17), 3.52-3.60 (m, 1H) (H16), 3.36-3.45 (m, 1H) (H13), 3.21-3.30 (m, 1H) (H2), 2.71-2.84 (m, 2H) (H24), 2.20-2.45 (m, 6H) (H20a, H19, H11a and –OH x 3), 1.75-1.94 (m, 3H) (H11b, H12a, H20b), 1.72 (s, 3H) (H27), 1.51-1.68 (m, 1H) (H15a, overlapping w/water), 1.21-1.51 (m, 4H) (H12b, H14a, H14b, H15b), 1.25 (d, *J* = 6.8 Hz, 3H) (H30), 0.92 (d, *J* = 6.8 Hz, 3H) (H29); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.4, 144.4, 144.0, 135.1, 135.0, 134.1, 133.3, 131.4, 131.4, 129.4, 127.9, 115.7, 110.7, 79.9, 78.3, 78.0, 77.6, 76.7 (overlapping w/chloroform), 73.2, 44.1, 41.2, 36.0, 32.6, 32.3, 29.9, 28.9, 27.1, 22.5, 17.5, 15.3; IR (neat) 3439, 2929, 1731, 1454, 1168, 990 cm^{-1}; HRMS (ES+) *m/z* for $C_{30}H_{44}O_6Na$ $[M+Na]^+$ calcd 523.3036, found 523.3038.

19-*epi*-Amphidinolide E (3) series

Tricarbonyl[(*E*)-(2*S*,3*R*)-2-Methyl-hexa-3,5-dienoic acid (1*R*,2*S*)-1-((*R*)-{(2*S*,5*S*)-5-[(*E*)-4-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-[1,3]dioxolan-4-yl)-but-3-enyl]-tetrahydro-furan-2-yl}-triethylsilanyloxy-methyl)-2-methyl-pent-4-ynyl ester]iron (78)

Esterification of alcohol 67 with acid **9** was accomplished using a procedure analogous to that outlined for **39**: alcohol **67** (0.34 g, 0.68 mmol), acid **9** (0.29 g, 1.09 mmol), triethylamine (0.35 mL, 2.4 mmol), DMAP (83 mg, 0.68 mmol), THF (1.5 mL) and 2,4,6-trichlorobenzoyl chloride (0.17 mL, 1.09 mmol) were used. Purification of the crude product by flash column chromatography afforded **78** (0.501 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ = +13° (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.84 (m, 2H), 5.39-5.49 (m, 2H), 5.34 (d, *J* = 17.6 Hz, 1H), 5.20-5.28 (m, 2H), 4.86 (d, *J* = 8.4 Hz, 1H), 4.02-4.09 (m, 2H), 3.68-3.78 (m, 2H), 3.61-3.68 (m, 1H), 2.06-2.40 (m, 6H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.72-1.90 (m, 3H), 1.46-1.70 (m, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 0.89-1.02 (m, 13H), 0.60-0.77 (m, 6H), 0.33 (bdd, *J* = 1.6, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 173.8, 136.2, 134.4, 126.1, 118.6, 108.9, 87.5, 82.4, 82.3, 81.7, 80.7, 78.7, 77.1, 75.3, 70.4, 64.1, 44.6, 40.5, 35.3, 32.9, 31.0, 29.3, 27.8, 27.2, 27.1, 22.6, 19.4, 15.9, 7.2, 5.5; IR (neat) 3311, 2936, 2049, 1979, 1731 cm^{-1}; HRMS (ESI-TOF+) *m/z* for $C_{38}H_{56}FeO_9SiH$ $[M+H]^+$ calcd 741.3116, found 741.3101.

(4*E*,11*E*,13*E*)-(1*S*,6*R*,10*R*,15*R*,18*R*,19*R*,20*S*)-18-((*S*)-3-Iodo-1-methyl-but-3-enyl)-8,8,15-trimethyl-19-triethylsilanyloxy-7,9,17,23-tetraoxa-tricyclo[18.2.1.0^{6,10}]tricosa-4,11,13-trien-16-one (79)

The oxidative decomplexation of 78 was accomplished using a procedure analogous to that outlined for the conversion of 39 to 40: ester 78 (0.45 g, 0.60 mmol), acetone (6 mL) and cerium ammonium nitrate (CAN) (0.66 g, 1.2 mmol) were used. The crude product was purified by flash column chromatography to afford the polyene product (0.30 g, 82%) as a colorless oil: $[\alpha]^{25}_D$ = −7.3° (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (dt, *J* = 10.4, 16.8, 1H), 6.15 (dd, *J* = 10.8, 15.6 Hz, 1H), 5.74-5.84 (m, 3H), 5.43 (bdd, *J* = 5.6, 14.4 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.17 (d, *J* = 16.4, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.86 (dd, *J* = 2.4, 8.0 Hz, 1H), 4.02-4.09 (m, 2H), 3.60-3.77 (m, 1H), 3.22 (quint., *J* = 7.2 Hz, 1H), 2.31-2.41 (m, 1H), 2.04-2.26 (m, 4H), 1.98 (t, *J* = 2.8 Hz, 1H), 1.72-1.91 (m, 2H), 1.58-1.69 (m, 1H), 1.39-1.57 (m, 3H), 1.44 (s, 3H), 1.44 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.57-0.74 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 136.5, 136.2, 134.4, 132.7, 132.3, 126.0, 118.5, 117.1, 108.9, 82.3, 82.3, 81.9, 80.5, 78.6, 77.0, 75.2, 70.2, 43.0, 35.3, 33.0, 31.0, 29.3, 27.6, 27.1, 27.0, 22.7, 17.2, 15.7, 7.1, 5.4; IR (neat) 3309, 2953, 1983, 1734, 1239, 1169, 1054 cm^{-1}; HRMS (ESI-TOF+) *m/z* for $C_{35}H_{56}O_6SiNa$ $[M+Na]^+$ calcd 623.3744, found 623.3728.

Ring closing metathesis of the polyene was accomplished using a procedure analogous to that outlined for the conversion of **39** to **40**: polyene from the preceding step (124 mg, 0.206 mmol), dichloromethane (206 mL) and Grubbs' first generation catalyst (17 mg, 0.021 mmol) were used. The crude product was purified by flash column chromatography to afford the macrocycle product (67 mg, 57%) as a colorless oil. In addition, an inseparable mixture of products thought to arrive by enyne metathesis (6 mg, 5%) was also isolated. Spectroscopic data for the macrocycle product: $[\alpha]^{25}_{D} = -44°$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14-6.26 (m, 2H), 5.71 (ddd, *J* = 3.2, 9.6, 14.4 Hz, 1H), 5.48-5.58 (m, 2H), 5.32 (dd, *J* = 8.8, 15.2 Hz, 1H), 4.76 (d, *J* = 8.0 Hz, 1H), 4.01 (app dt, *J* = 8.4, 25.2 Hz, 2H), 3.73 (d, *J* = 8.4 Hz, 1H), 3.18-3.34 (m, 3H), 2.15-2.36 (m, 4H), 1.98 (t, *J* = 2.0 Hz, 1H), 1.82-1.96 (m, 2H), 1.61-1.70 (m, 1H), 1.48-1.57 (m, 1H), 1.38-1.48 (m, 1H), 1.42 (s, 3H), 1.42 (s, 3H), 1.10-1.28 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.54-0.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 138.5, 136.1, 135.8, 131.3, 127.7, 125.8, 109.1, 83.2, 82.5, 81.4, 80.1, 77.9, 75.1, 70.4, 44.4, 32.1, 29.6, 28.7, 27.3, 27.2, 27.1, 22.2, 17.0, 16.0, 7.3, 5.8; IR (neat) 3310, 2935, 1732, 1237, 1170 cm^{-1}; HRMS (ESI-TOF+) *m/z* for $C_{33}H_{52}O_6SiH$ $[M+H]^+$ calcd 573.3606, found 573.3596.

Stannylalumination-protonolysis of the macrocycle alkyne was accomplished using a procedure analogous to that outlined for the conversion of **40** to **41**: macrocycle alkyne from above (32 mg, 0.056 mmol), THF (1 mL), Bu_3Sn-$AlEt_2$ (0.80 mL of the 0.42M solution, 0.34 mmol) and CuCN (1 mg, 0.011 mmol) were used. Purification of the crude product by flash column chromatography afforded the vinylstannane (31 mg, 64%) as a colorless oil: $[\alpha]^{25}_{D} = -119°$ (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15-6.28 (m, 2H), 5.67-5.76 (m, 2H), 5.53 (app dd, *J* = 9.6, 14.4 Hz, 2H), 5.33 (dd, *J* = 8.8, 15.6 Hz, 1H), 5.20 (t, $^3J_{Sn\text{-}H}$ = 32.0 Hz, 1H), 4.57 (d, *J* = 7.6 Hz, 1H), 4.02 (app dt, *J* = 8.8, 23.2 Hz, 2H), 3.72 (app q, *J* = 12.4 Hz, 1H), 3.19-3.36 (m, 3H), 2.49 (bd, *J* = 13.6 Hz, 1H), 2.28-2.36 (m, 1H), 2.10-2.20 (m, 1H), 1.83-2.24 (m, 3H), 1.56-1.71 (m, 1H), 1.40-1.56 (m, 9H), 1.43 (s, 3H), 1.43 (s, 3H), 1.25-1.36 (m, 7H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 9H), 0.85-0.92 (m, 14H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.59-0.69 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 152.9, 138.6, 136.2, 136.0, 131.3, 127.6, 126.6, 125.8, 109.1, 83.2, 82.5, 80.3, 80.0, 77.5, 75.9, 44.4, 44.0, 33.1, 32.3, 29.7, 29.4, 29.3, 28.7, 27.5, 27.3, 27.2, 17.1, 15.7, 13.8, 9.6, 7.4, 5.8; IR (neat) 2955, 1732, 1171, 1054 cm^{-1}; HRMS (ESI-TOF+) *m/z* for $C_{45}H_{80}O_6SiSnH$ $[M+H]^+$ calcd 865.4819, found 865.4825.

Iododestannylation of vinylstannane was accomplished using a procedure analogous to that outlined for the conversion of **40** to **41**: vinylstannane from the preceding step (54 mg, 0.063 mmol), dichloromethane (2 mL) and NIS (17 mg, 0.075 mmol) were used. The crude product was purified by flash column chromatography to afford **79** (34 mg, 77%) as a colorless oil: $[\alpha]^{25}_{D} = -110°$ (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15-6.28 (m, 2H), 6.09 (s, 1H), 5.76 (s, 1H), 5.72 (ddd, *J* = 3.6, 9.6, 15.2 Hz, 1H), 5.48-5.58 (m, 2H), 5.33 (dd, *J* = 8.8, 15.2 Hz, 1H), 4.60 (d, *J* = 7.6 Hz, 1H), 4.02 (app dt, *J* = 8.4, 25.2 Hz, 2H), 3.68 (d, *J* = 8.8 Hz, 1H), 3.30-3.38 (m, 1H), 3.19-3.30 (m, 2H), 2.63 (dd, *J* = 4.4, 13.6 Hz, 1H), 2.26-2.39 (m, 2H), 2.12 (dd, *J* = 9.2, 13.6 Hz, 1H), 1.84-2.10 (m, 2H), 1.36-1.55 (m, 2H), 1.43 (s, 3H), 1.43 (s, 3H), 1.11-1.27 (m, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.6 Hz, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.60-0.71 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 138.6, 136.2, 135.7, 131.5, 127.7, 127.5, 125.8, 110.7, 109.2, 83.1, 82.5, 80.1, 77.7, 77.6, 75.9, 48.5, 44.3, 33.3, 32.2, 29.6, 28.7, 27.3, 27.2, 27.2, 17.0, 15.0, 7.4, 5.8; IR (neat) 2981, 1731, 1377, 1170, 1053 cm^{-1}; HRMS (ESI-TOF+) *m/z* for $C_{33}H_{53}IO_6SiH$ $[M+H]^+$ calcd 701.2729, found 701.2723.

19-*epi*-amphidinolide E (3)

Deprotection of **79** was accomplished using a procedure analogous to that outlined for the conversion of **41** to **2**: vinyl iodide **79** (34 mg, 0.049 mmol) and AcOH, THF and water (4/1/1)

(1 mL) were used. The crude product was purified by flash column chromatography to afford only the C18 lactone (24 mg, 90%) as a colorless oil: $[\alpha]^{25}_{D} = -90°$ (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10-6.26 (m, 2H), 6.08 (s, 1H), 5.76 (s, 1H), 5.49-5.69 (m, 3H), 5.26 (dd, *J* = 8.0, 15.2 Hz, 1H), 4.75 (d, *J* = 8.0 Hz, 1H), 3.91 (app dt, *J* = 8.8, 26.0 Hz, 2H), 3.63-3.68 (m, 1H), 3.58-3.60 (m, 1H), 3.34-3.46 (m, 1H), 3.21-3.30 (m, 1H), 2.66 (dd, *J* = 3.6, 13.6 Hz, 1H), 2.33-2.50 (m, 4H), 2.20-2.29 (m, 1H), 2.14 (app dd, *J* = 9.6, 14.0 Hz, 1H), 1.70-1.93 (m, 3H), 1.54-1.64 (m, 1H), 1.32-1.49 (m, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 135.0, 134.3, 131.6, 131.6, 129.6, 127.6, 110.5, 80.0, 78.3, 77.7, 76.2, 73.4, 48.3, 44.1, 33.9, 32.9, 30.1, 29.1, 27.2, 17.6, 15.0; IR (neat) 3430, 2933, 1731, 1169, 990 cm^{-1}; HRMS (ES+) *m/z* for $C_{24}H_{35}IO_6Na$ $[M+Na]^+$ calcd 569.1376, found 569.1367.

Stille coupling of the C18 lactone from was accomplished using a procedure analogous to that outlined for the conversion of **41** to **2**: vinyl iodide from above (24 mg, 0.044 mmol), CuCl (24 mg, 0.24 mmol), THF (0.5 mL), vinylstannane **6** (82 mg, 0.22 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.0087 mmol) were used. The crude product was purified by flash column chromatography using 10% methanol/chloroform to afford material that was still contaminated with an organotin impurity. The stannane impurity was removed by HPLC purification with 100% ethyl acetate eluent on a normal phase, Varian Dynamax Microsorb 60-8 Si, 250 × 21.4 mm column. The retention time for 19-*epi*-amphidinolide E was 7.5 min. The flow rate was 18 mL/min. 19-*epi*-Amphidinolide E was detected using UV absorption (λ = 254 nm and 280 nm) and RI detection. Using the above conditions 15 mg (68%) of pure 19-*epi*-amphidinolide E (**3**) was isolated: $[\alpha]^{25}_{D} = -7.8°$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10-6.28 (m, 2H), 6.05 (d, *J* = 15.6 Hz, 1H), 5.87 (dt, *J* = 6.8, 16.0 Hz, 1H), 5.49-5.70 (m, 3H), 5.27 (dd, *J* = 8.0, 15.2 Hz, 1H), 4.98 (s, 1H), 4.88 (s, 1H), 4.73 (s, 1H), 4.70 (s, 1H), 4.68 (d, *J* = 10.4 Hz, 1H), 3.95 (t, *J* = 8.4 Hz, 1H), 3.88 (t, *J* = 8.8 Hz, 1H), 3.78 (app q, *J* = 8.8 Hz, 1H), 3.35-3.44 (m, 1H), 3.21-3.31 (m, 1H), 2.77 (d, *J* = 6.8 Hz, 2H), 2.62 (dd, *J* = 3.6, 13.2 Hz, 1H), 2.24-2.46 (m, 5H), 1.74-1.94 (m, 4H), 1.71 (s, 3H), 1.53-1.64 (m, 1H), 1.22-1.51 (m, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 144.8, 143.9, 135.4, 135.1, 134.3, 133.1, 131.6, 129.6, 128.5, 116.3, 111.0, 80.1, 78.2, 78.0, 77.7, 76.8, 73.4, 44.2, 41.6, 36.0, 32.5, 32.2, 30.0, 29.1, 27.1, 22.7, 17.5, 15.7; IR (neat) 3400, 2931, 1731, 1169, 989 cm^{-1}; HRMS (ESI-TOF+) *m/z* for $C_{30}H_{44}O_6Na$ $[M+Na]^+$ calcd 523.3036, found 523.3024.

Acknowledgements

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substituted phenol: Fürstner A, Aissa C, Chevrier C, Teply F, Nevado C, Tremblay M. Angew Chem, Int Ed 2006;45:5832.. Although it is possible that acid 13 (Table 2) could have suffered from a similar side-reaction pathway, the expect side product(s) (ortho-methylphenol or acylated ortho-methylphenol) was not observed

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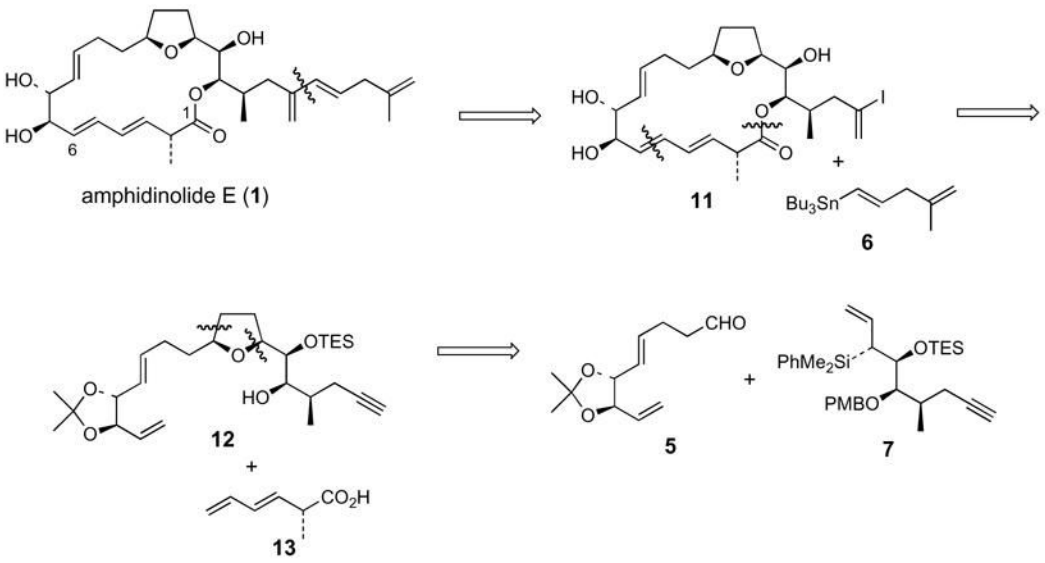


Figure 1. Retrosynthetic analysis of amphidinolide E

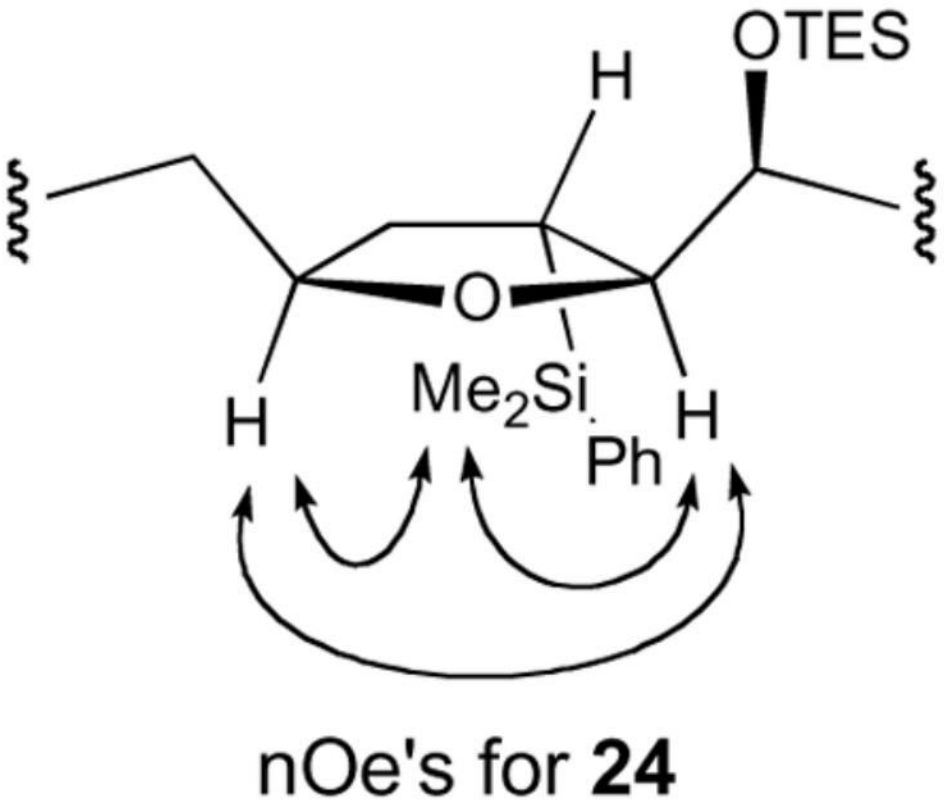


Figure 2. nOe analysis of 24

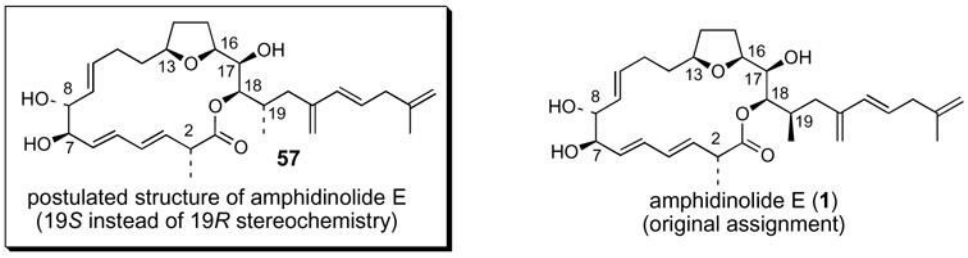
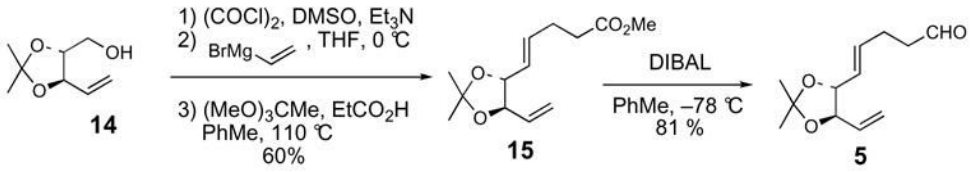
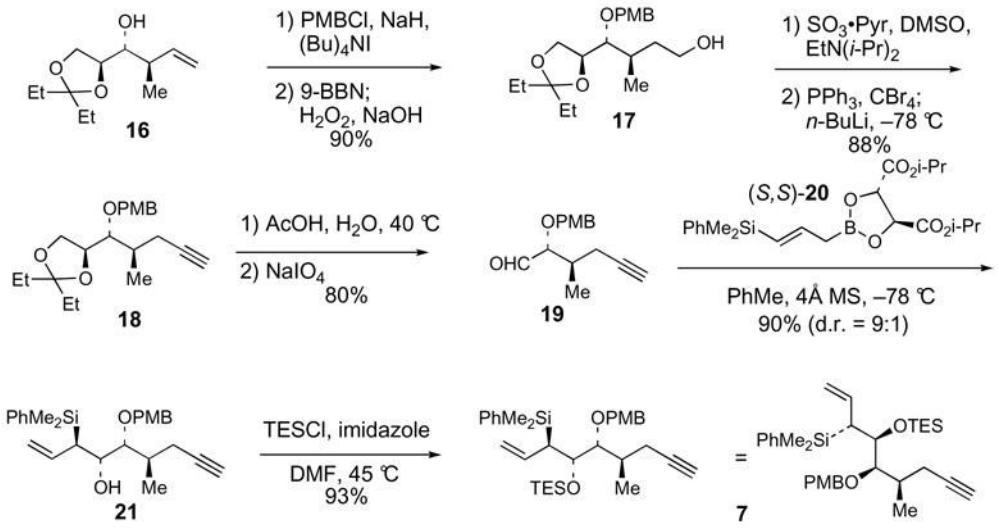


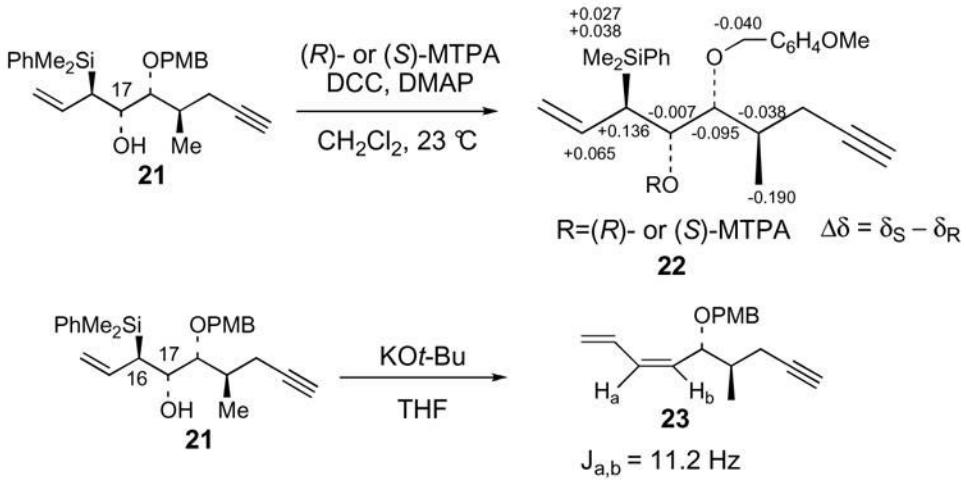
Figure 3. Postulated revised structure of amphidinolide E



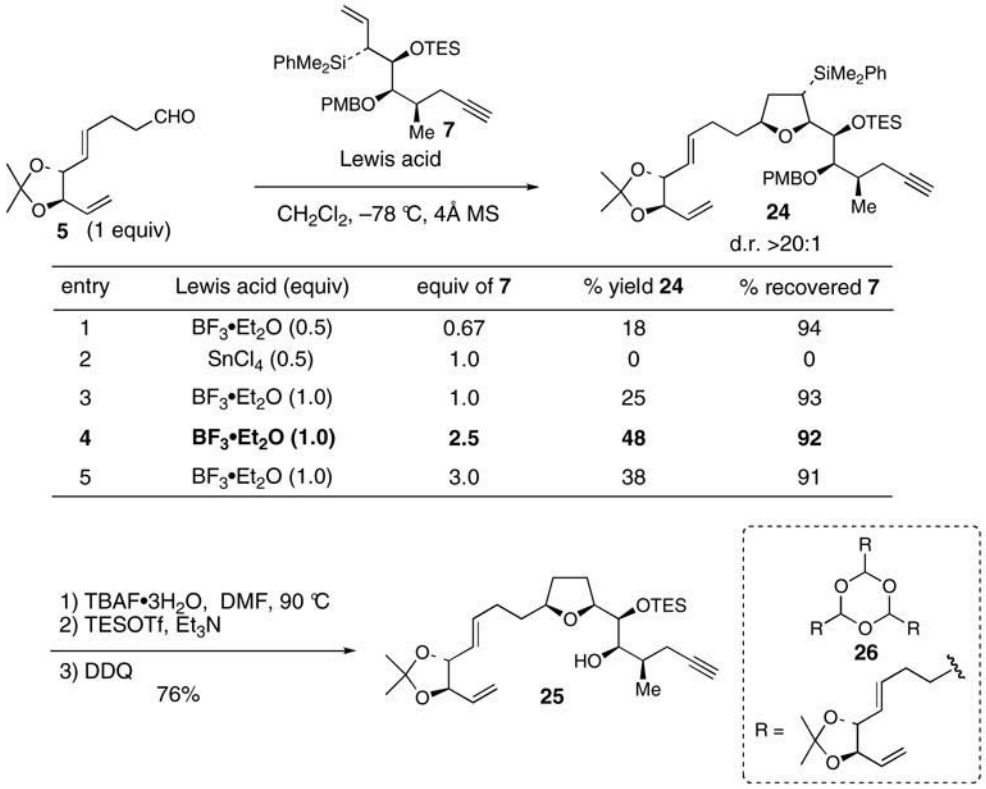
Scheme 1. Synthesis of aldehyde 5



Scheme 2. Synthesis of allylsilane 7

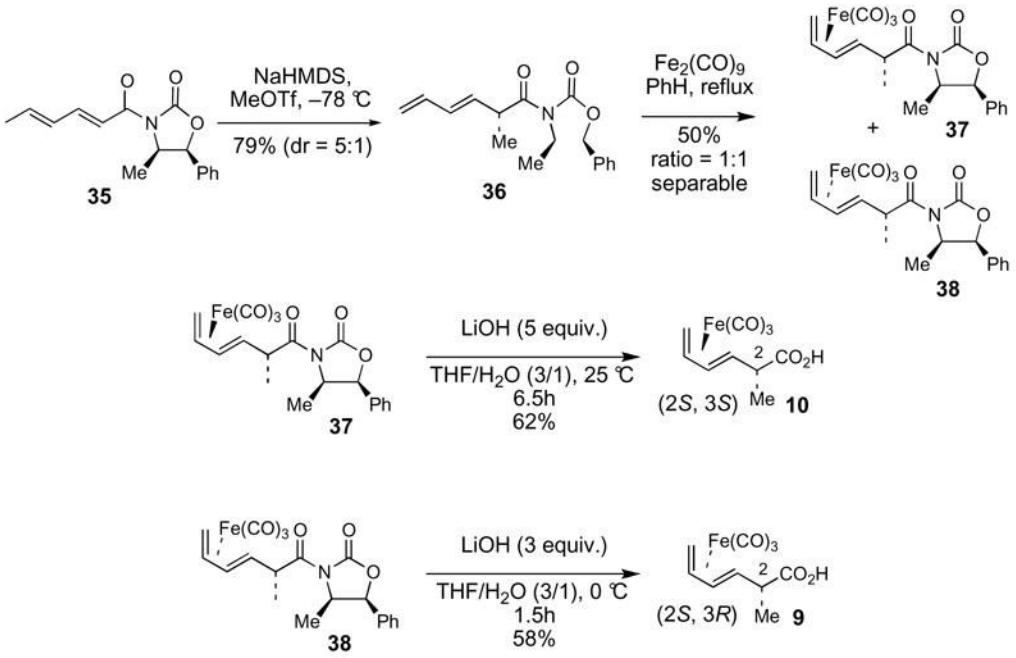


Scheme 3. Assignment of the C17 absolute and C16-C17 relative stereochemistry of allylsilane 21

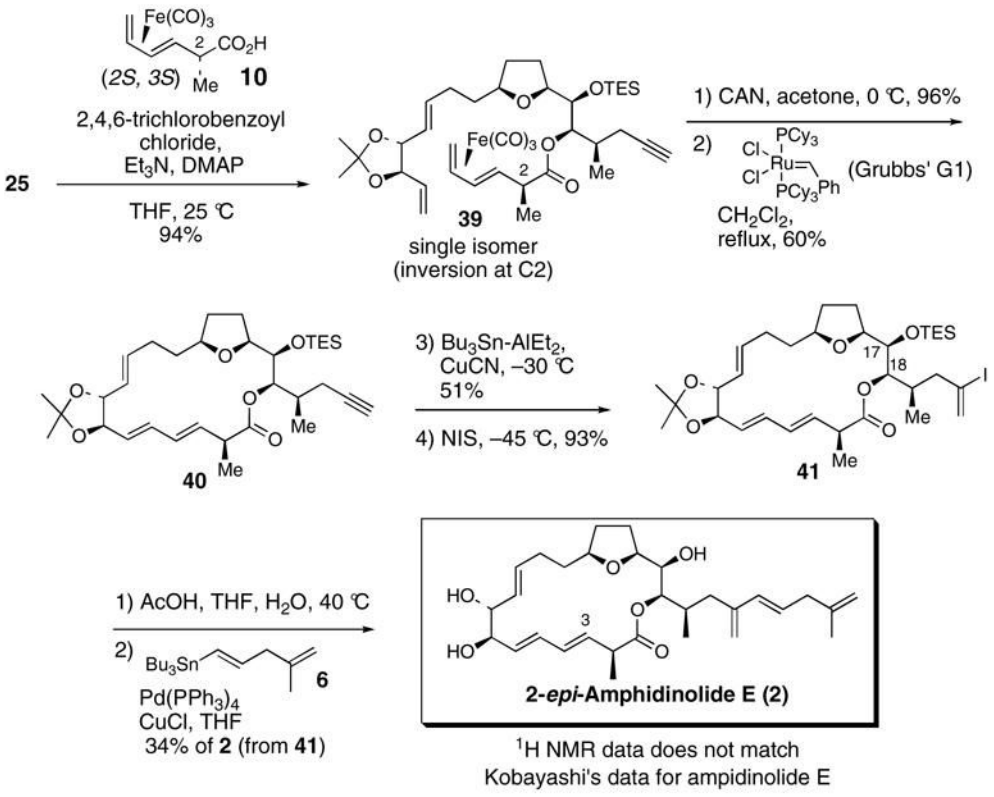


entry	Lewis acid (equiv)	equiv of **7**	% yield **24**	% recovered **7**
1	BF_3•Et_2O (0.5)	0.67	18	94
2	$SnCl_4$ (0.5)	1.0	0	0
3	BF_3•Et_2O (1.0)	1.0	25	93
4	**BF_3•Et_2O (1.0)**	**2.5**	**48**	**92**
5	BF_3•Et_2O (1.0)	3.0	38	91

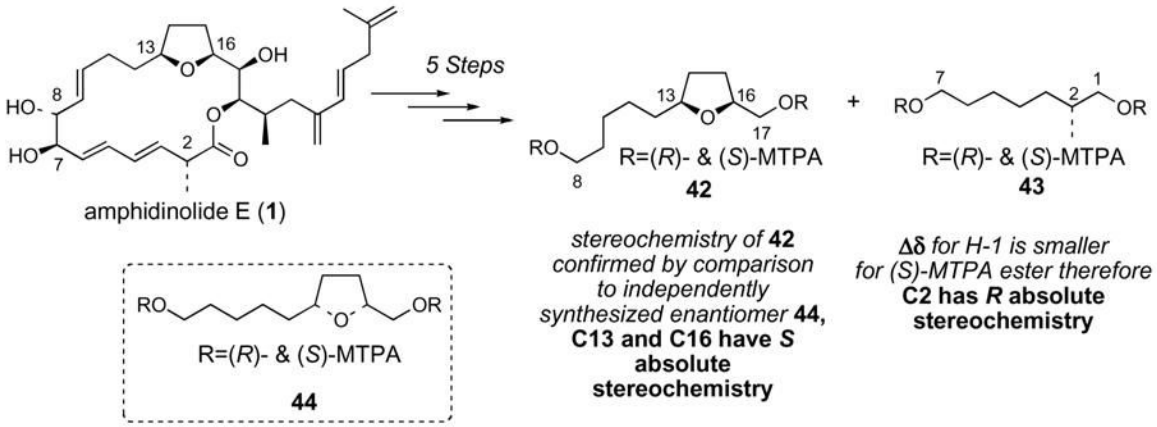
Scheme 4. [3+2] annulation of 5 and 7



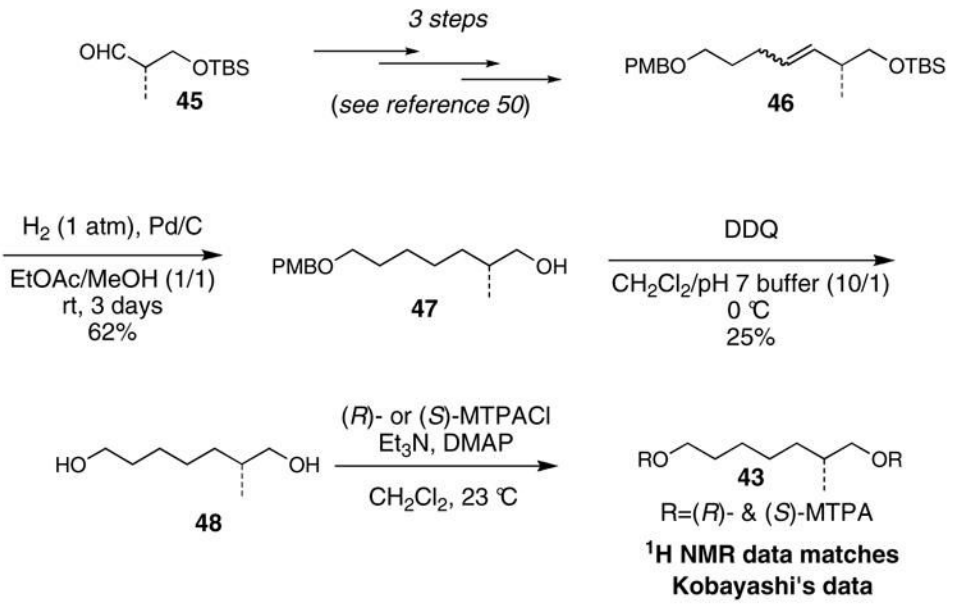
Scheme 5. Synthesis of acids 9 and 10



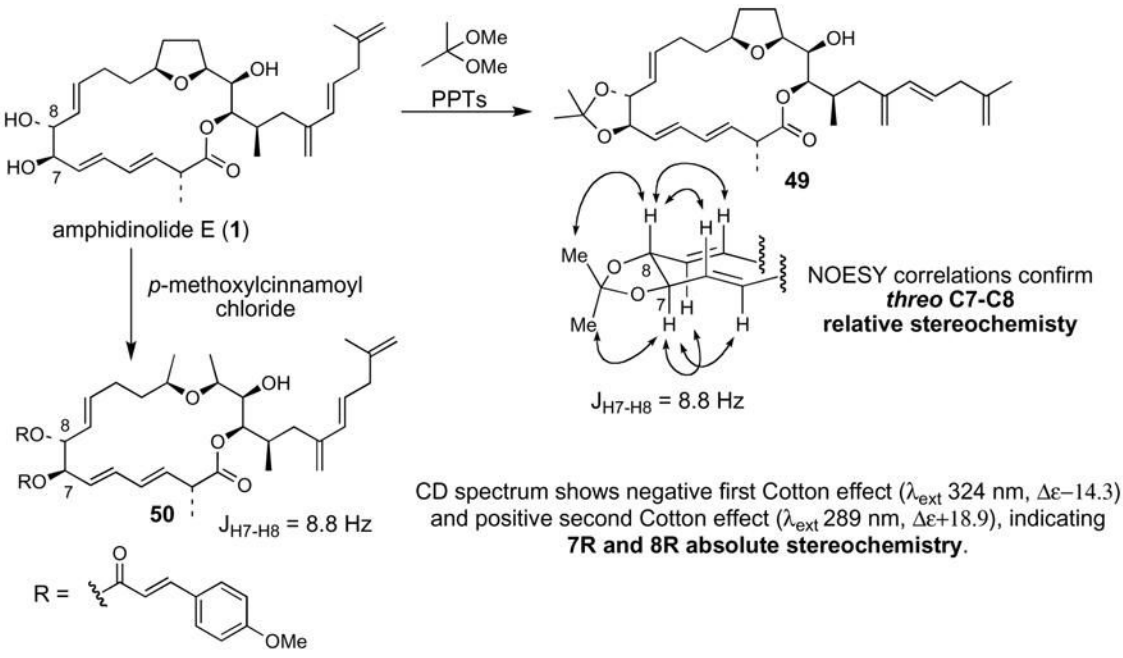
Scheme 6. Completion of 2-*epi*-amphidinolide E synthesis



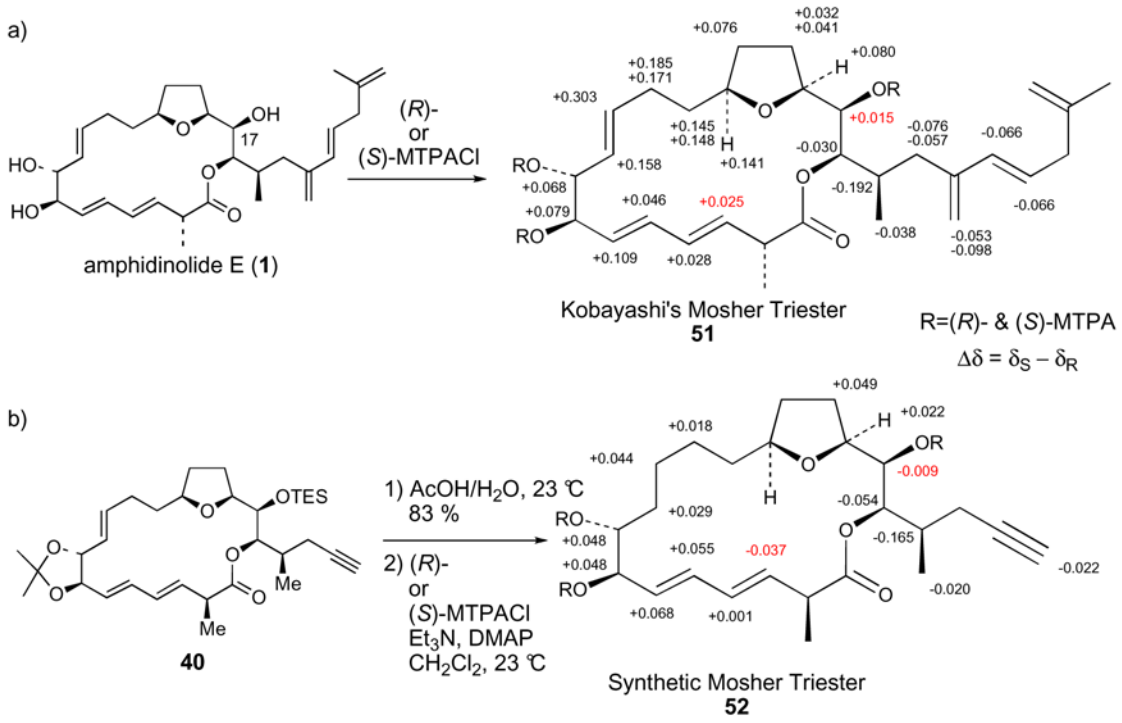
Scheme 7. Kobayashi's absolute stereochemical assignment of 13*S*, 16*S*, and 2*R*



Scheme 8. Synthetic confirmation of 2*R* stereochemistry of 43

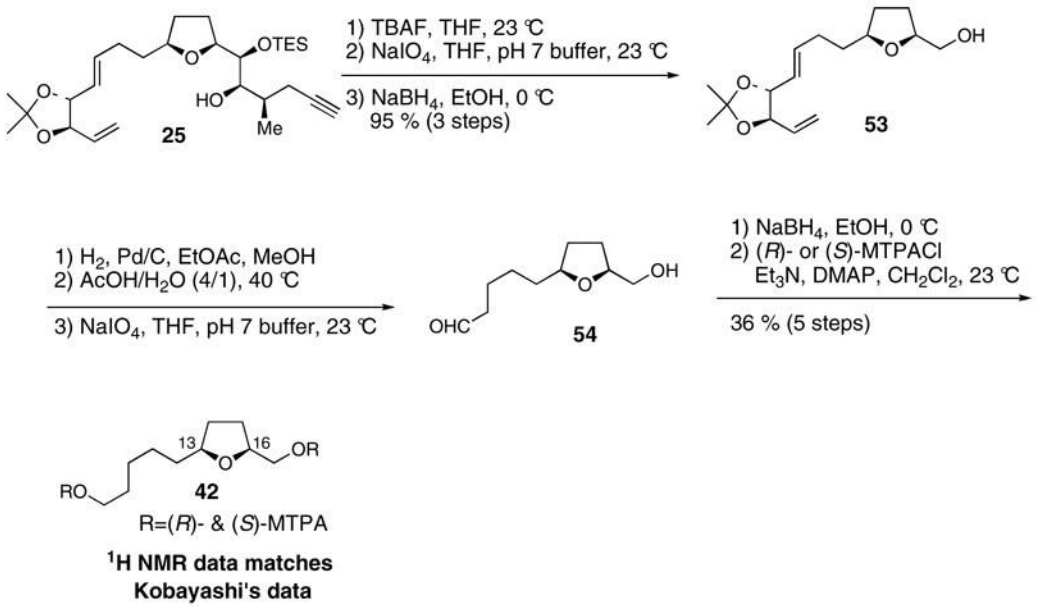


Scheme 9. Kobayashi's relative and absolute stereochemical assignment of C7 and C8

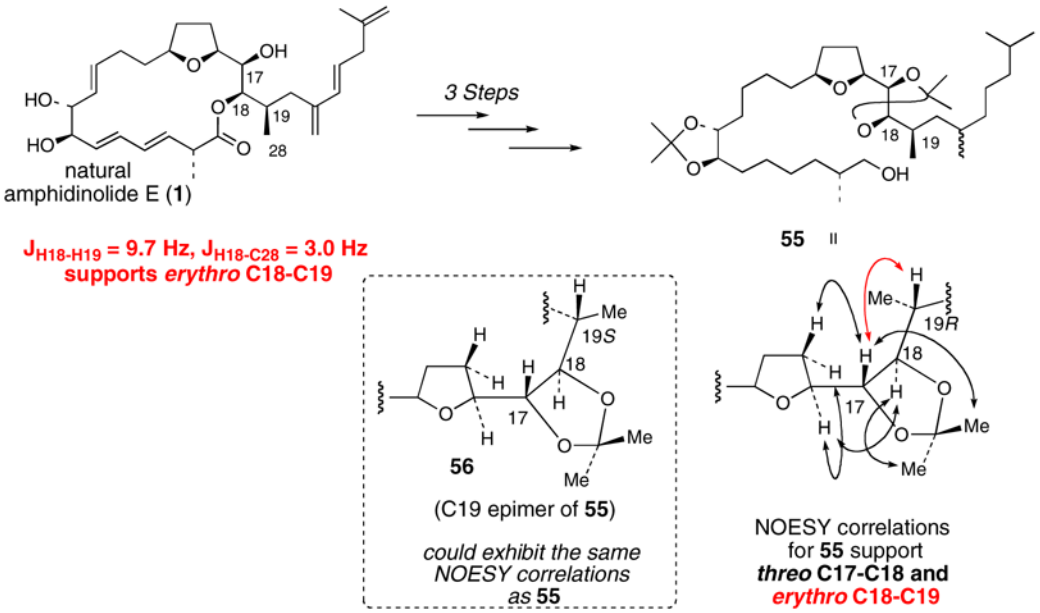


Scheme 10.

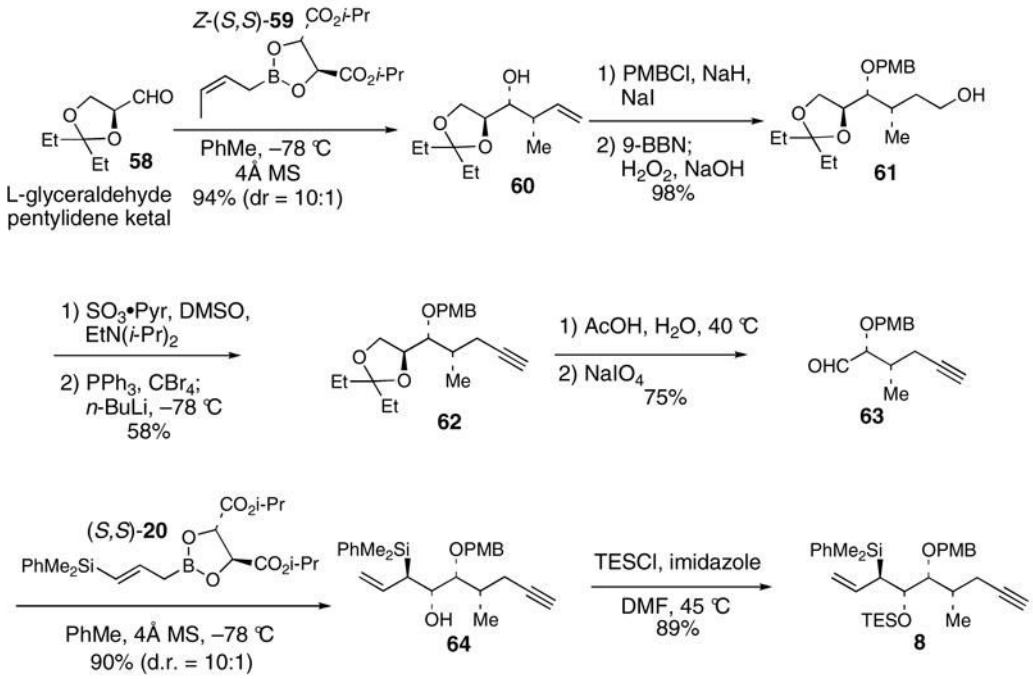
a) Kobayashi's absolute stereochemical assignment of C17 (also confirming C7 and C8). b) Comparison of Mosher ester data for synthetic **52** and natural product derivative **51**.



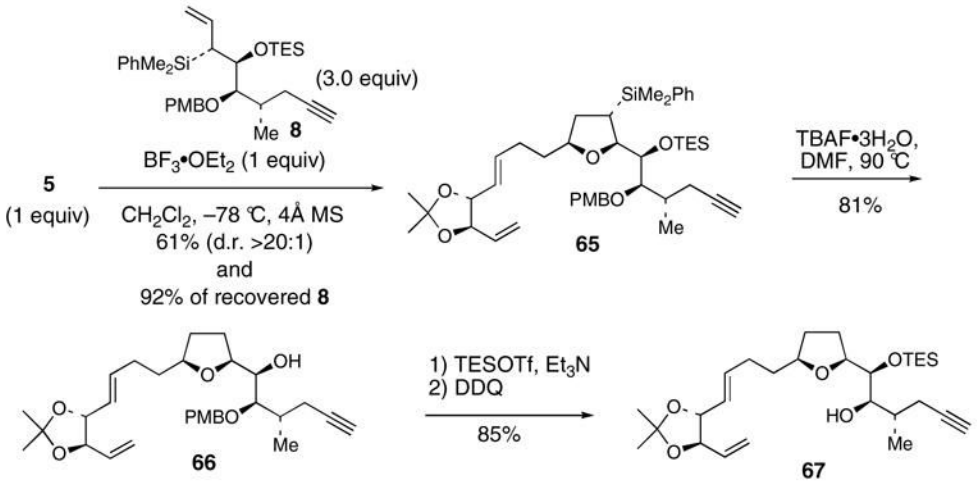
Scheme 11. Confirmation of 13*S* and 16*S* stereochemistry of 25



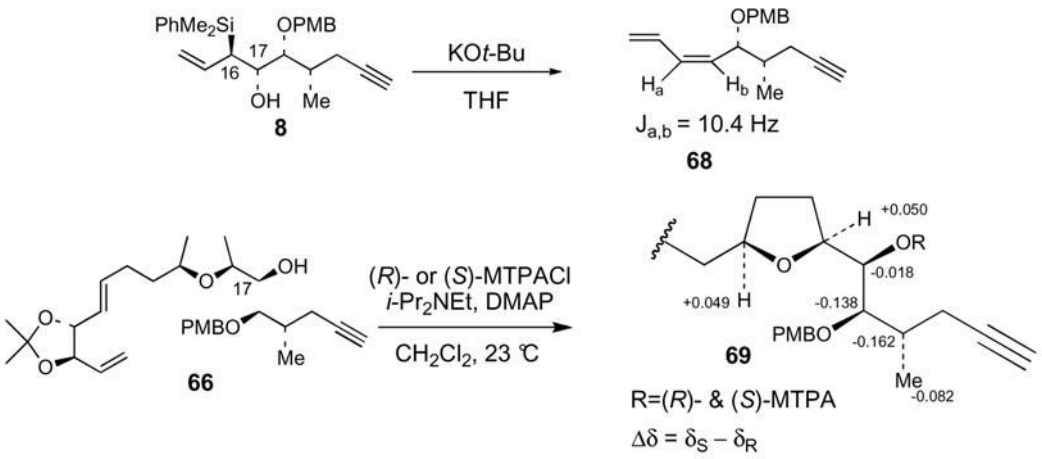
Scheme 12. Kobayashi's C17-C18 and C18-C19 relative stereochemical assignment



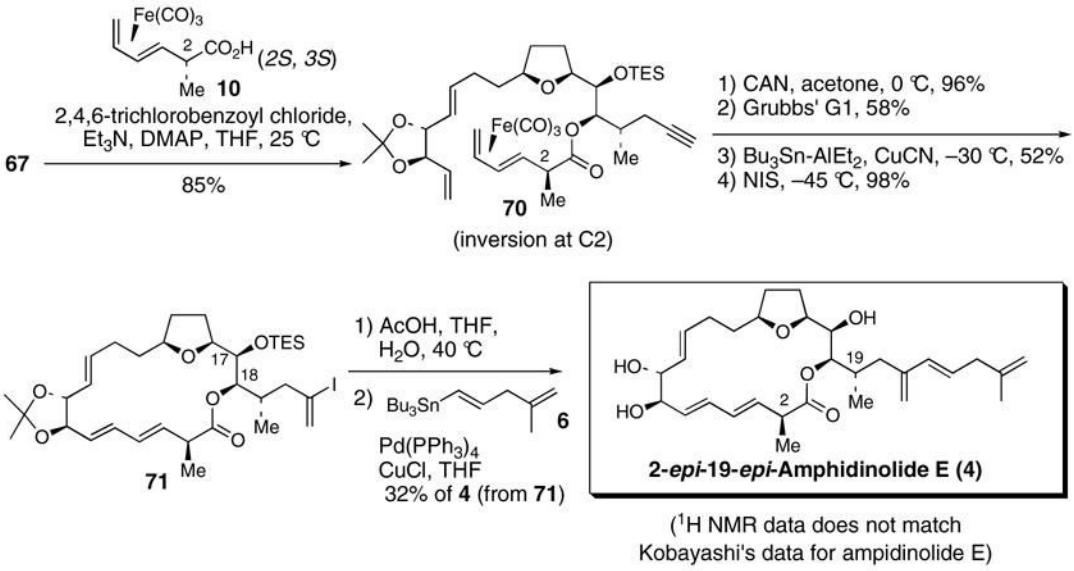
Scheme 13. Synthesis of 19-*epi*-allylsilane 8



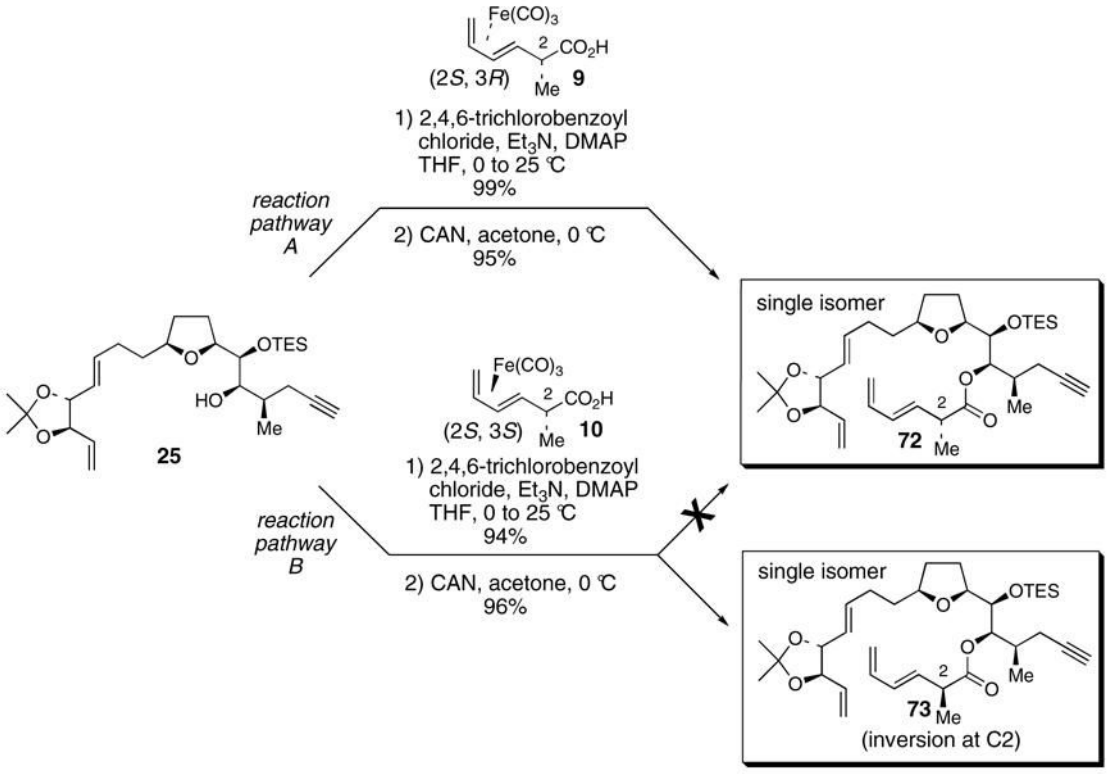
Scheme 14. [3+2] Annulation of 5 and 8



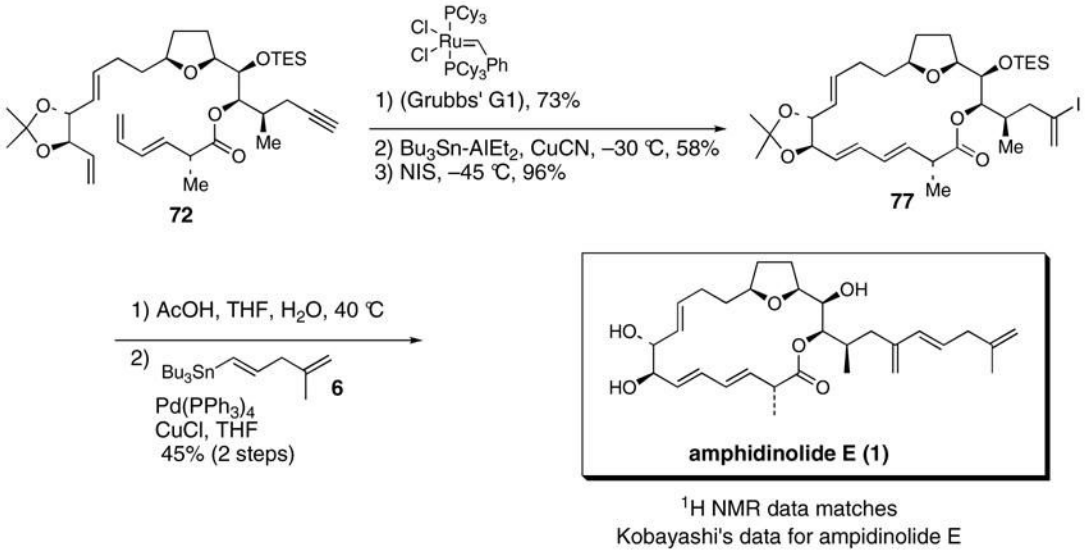
Scheme 15. Confirmation of the C16-C17 relative and C17 absolute stereochemistry



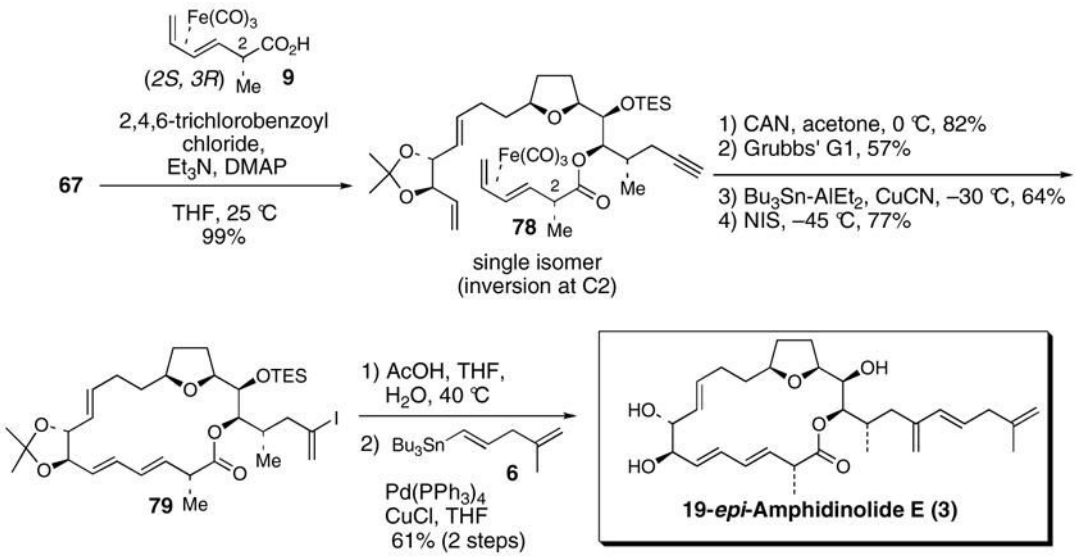
Scheme 16. Completion of 2-*epi*-19-*epi*-amphidinolide E synthesis



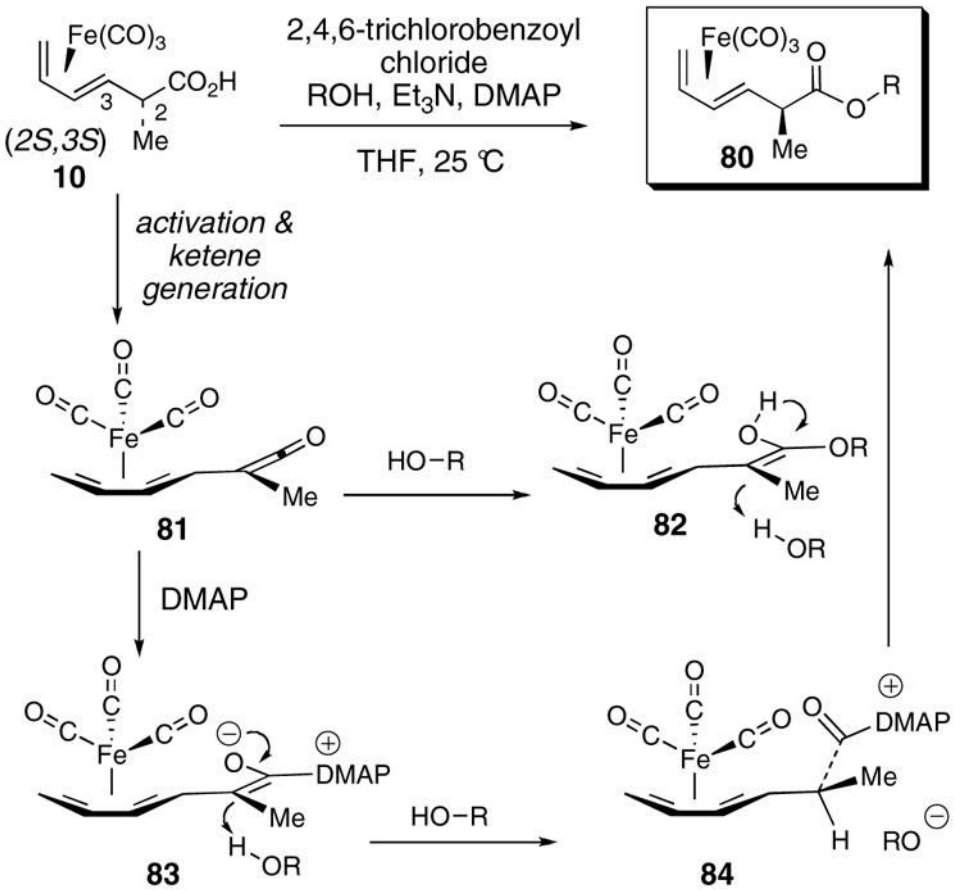
Scheme 17. Divergent behavior of acids 9 and 10 in the modified Yamaguchi esterification reaction of 25



Scheme 18. Completion of the synthesis of amphidinolide E



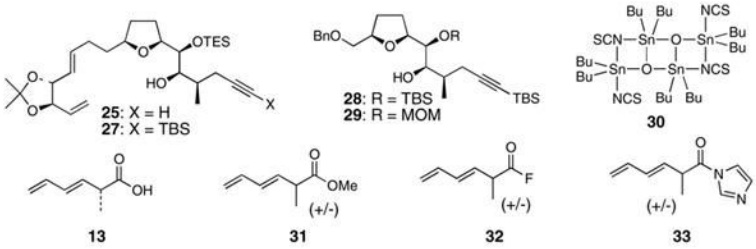
Scheme 19. Completion of the synthesis of 19-*epi*-amphidinolide E



Scheme 20. Proposed esterification pathway

Table 1

Attempted esterification reactions



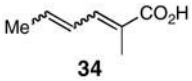
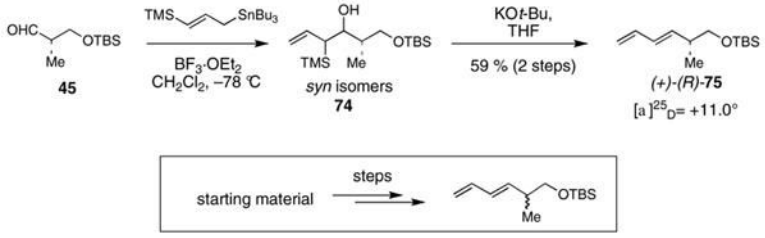
entry	reaction	conditions	Results	
1	**27** + **13**	2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, rt to reflux	decomposition of acid ↓	isolated:  **34**
2	**27** + **13**	EDCI•MeI, DMAP, CH_2Cl_2, 0 to 23 °C		
3	**28** + **13**	PyBrOP, *i*-Pr_2NEt, CH_2Cl_2, 0 to 23 °C		
4	**28** + **33**	Tol., 23 to 100 °C		
5	**28** + **31**	**30** (10 mol %), Tol., 50 °C		
6	**29** + **13**	DCC, HOBt, THF, 23 to 50 °C		
7	**29** + **32**	**29,** $(Bu_3Sn)_2O$, PhH, reflux; then add **32**, CH_2Cl_2		
8	**29** + **32**	**29**, LDA, −78 °C, THF; then **32** or **33**, THF		
9	**25** + **13**	**13**, HCCOEt, $\{RuCl_2(p\text{-cymene})\}_2$, PhMe, 0 to 23°C; then add **25**, CSA (10 mol %), PhMe, 50 °C		

Table 2

Assessment of C2 stereochemistry of 36, 9, 10, 76, and 39



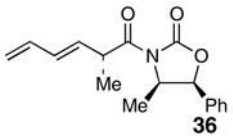
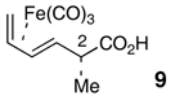
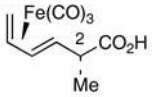
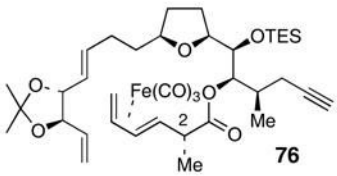
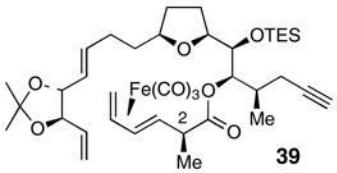
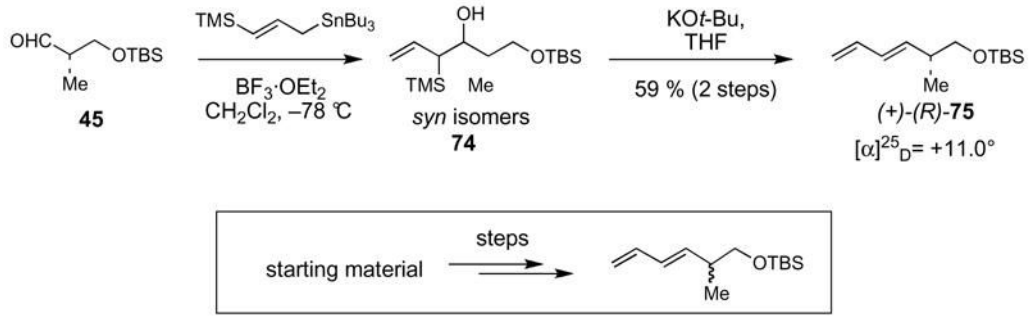
entry	starting material	steps	overall yield	product [(+)- or (−)-75]
1	 36	1) LAH 2) TBSCl, Imidazole	76%	(+)-(*R*)-**75**
2	 9	1) BH_3·SMe_2, THF 2) TBSCl, Imidazole 3) CAN	84%	(+)-(*R*)-**75**
3	 10	1) BH_3·SMe_2, THF 2) TBSCl, Imidazole 3) CAN	68%	(+)-(*R*)-**75**
4	 76	1) DIBAL, −78 °C 2) TBSCl, Imidazole 3) CAN	56%	(+)-(*R*)-**75**
5	 39	1) DIBAL, −78 °C 2) TBSCl, Imidazole 3) CAN	61%	(−)-(*S*)-**75**

Table 3

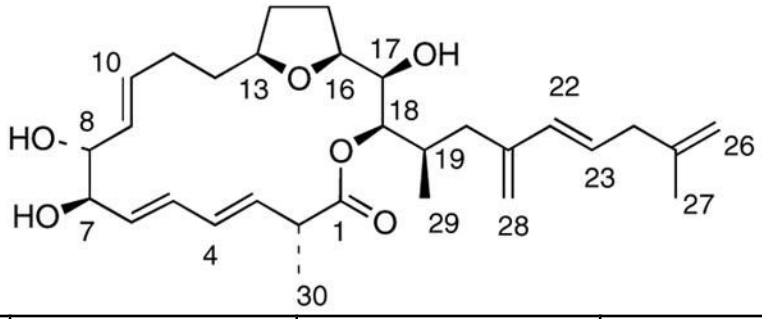
Spectroscopic comparison of natural and synthetic amphidinolide E (1) ^{1}H NMR Data



Proton	Natural (Kobayashi, 600 MHz)	Synthetic (Roush, 400 MHz)
2	3.26 (1H, dq, J = 10.0, 6.8 Hz)	3.26 (1H, m)
3	5.59 (1H, dd, J = 14.0, 10.0)	5.59 (1H, m) *H3, H10 & H23 overlap*
4	6.20 (1H, dd, J = 14.0, 10.6)	6.20 (1H, m) *H4 and H5 overlap*
5	6.16 (1H, dd, J = 14.5, 10.6)	6.16 (1H, m) *H4 and H5 overlap*
6	5.53 (1H, dd, J = 14.5, 8.5)	5.53 (1H, dd, J = 14.8, 8.8)
7	3.88 (1H, t, J = 8.5)	3.89 (1H, t, J = 8.8)
8	3.95 (1H, t, J = 8.5)	3.95 (1H, t, J = 8.4)
9	5.27 (1H, dd, J = 15.6, 8.5)	5.27 (1H, dd, J = 14.4, 7.6)
10	5.64 (1H, m)	5.64 (1H, m) *H3, H10 & H23 overlap*
11a	2.23 (1H, m)	2.23 (1H, m)
11b	1.82 (1H, m)	1.82 (1H, m)
12a	1.76 (1H, m)	1.76 (1H, m)
12b	1.48 (1H, m)	1.48 (1H, m)
13	3.41 (1H, m)	3.40 (1H, m)
14a	1.40 (1H, m)	1.40 (1H, m)
14b	1.25 (1H, m)	1.25 (1H, m)
15a	1.58 (1H, m)	1.58 (1H, m) *overlapping w/water*
15b	1.33 (1H, m)	1.33 (1H, m)
16	3.56 (1H, dt, J = 7.5, 7.1)	3.56 (1H, m)
17	3.72 (1H, dt, J = 7.5, 4.5)	3.72 (1H, m)
18	4.66 (1H, d, J = 8.3)	4.66 (1H, d, J = 9.2)
19	2.25 (1H, m)	2.25 (1H, m)
20a	2.40 (1H, d, J = 13.4)	2.40 (1H, d, J = 14.0)
20b	1.79 (1H, m)	1.79 (1H, m)
22	6.05 (1H, d, J = 15.9)	6.05 (1H, d, J = 15.2)
23	5.71 (1H, dt, J = 15.9, 6.8)	5.71 (1H, m) *H3, H10 & H23 overlap*
24	2.78 (2H, br d, J = 6.8)	2.78 (2H, m)
26a	4.75 (1H, s)	4.75 (1H, s)
26b	4.71 (1H, s)	4.71 (1H, s)
27	1.72 (3H, s)	1.72 (3H, s)
28a	4.98 (1H, s)	4.98 (1H, s)
28b	4.87 (1H, s)	4.87 (1H, s)
29	0.92 (3H, d, J = 6.6)	0.92 (3H, d, J = 6.8)
30	1.25 (3H, d, J = 6.8)	1.25 (3H, d, J = 6.8)

Table 4

Partial spectroscopic details of the four amphidinolide E stereoisomers 1–4



C(H)	Synthetic Amphidinolide E (1)	2-*epi*-Amphidinolide E (2)	19-*epi*-Amphidinolide E (3)	2-*epi*-19-*epi*-Amphidinolide E (4)
2	3.26 (1H, m)	3.35 (1H, q, J = 5.2)	3.26 (1H, m)	3.34 (1H, m)
3	5.67 (3H, m) *3, 10, & 23 overlap*	6.00 (1H, m)	5.60 (3H, m) *3, 6, & 10 overlap*	5.98 (1H, m)
4	6.19 (2H, m) *4 & 5 overlap*	6.20 (2, m) *4 & 5 overlap*	6.19 (2, m) *4 & 5 overlap*	6.20 (2, m) *4 & 5 overlap*
5	6.19 (2H, m)	6.20 (2, m)	6.19 (2, m)	6.20 (2, m)
	4 & 5 overlap	*4 & 5 overlap*	*4 & 5 overlap*	*4 & 5 overlap*
6	5.53 (1H, dd, J = 14.4, 8.8)	6.00 (3H, m) *6, 10, & 23 overlap*	5.60 (3H, m) *3, 6, & 10 overlap*	5.63 (2H, m) *6 & 10 overlap*
7	3.89 (1H, t, J = 8.8)	3.95 (2H, app dt, J = 8.4, 19.2) *7 & 8 overlap*	3.88 (1H, t, J = 8.8)	3.96 (2H, m) *7 & 8 overlap*
8	3.95 (1H, t, J = 8.4)	3.95 (2H, app dt, J = 8.4, 19.2) *7 & 8 overlap*	3.95 (1H, t, J = 8.4)	3.96 (2H, m) *7 & 8 overlap*
9	5.27 (1H, dd, J = 14.4, 7.6)	5.27 (1H, dd, J = 7.6, 14.4)	5.27 (1H, dd, J = 8.0, 15.2)	5.30 (1H, dd, J = 7.6, 15.2)
10	5.67 (3H, m) *3, 10, & 23 overlap*	6.00 (3H, m) *6, 10, & 23 overlap*	5.60 (3H, m) *3, 6, & 10 overlap*	5.63 (2H, m) *6 & 10 overlap*
13	3.40 (1H, m)	3.43 (1H, m)	3.40 (1H, m)	3.42 (1H, m)
16	3.56 (1H, m)	3.50 (1H, m)	3.56 (1H, app q, J = 8.8)	3.50 (1H, m)
17	3.72 (1H, m)	3.69 (1H, app t, J = 5.2)	3.78 (1H, d, J = 7.2)	3.74 (1H, m)
18	4.66 (1H, d, J = 9.2)	4.66 (1H, d, J = 9.6)	4.68 (1H, d, J = 10.4)	4.69 (1H, d, J = 10.4)
22	6.05 (1H, d, J = 15.2)	6.04 (1H, d, J = 16.0)	6.05 (1H, d, J = 15.6)	6.05 (1H, d, J = 16.0)
23	5.67 (3H, m) *3, 10, & 23 overlap*	6.00 (3H, m) *6, 10, & 23 overlap*	5.87 (1H, dt, J = 6.8, 16.0)	5.85 (1H, dt, J = 7.2, 15.6)
26a	4.75 (1H, s)	4.74 (1H, s)	4.73 (1H, s)	4.74 (1H, s)
26b	4.71 (1H, s)	4.70 (1H, s)	4.70 (1H, s)	4.70 (1H, s)
27	1.72 (3H, s)	1.72 (3H, s)	1.71 (3H, s)	1.72 (3H, s)
28a	4.98 (1H, s)	4.98 (1H, s)	4.98 (1H, s)	4.98 (1H, s)
28b	4.87 (1H, s)	4.86 (1H, s)	4.88 (1H, s)	4.88 (1H, s)
29	0.92 (3H, d, J = 6.8)	0.91 (3H, d, J = 6.8)	0.81 (3H, d, J = 6.4)	0.82 (3H, d, J = 6.8)
30	1.25 (3H, d, J = 6.8)	1.34 (3H, d, J = 7.2)	1.25 (3H, d, J = 6.8)	1.34 (3H, d, J = 6.8)