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Total Synthesis and Revision of C6 Stereochemistry of (+)-Amphidinolide W

Arun K. Ghosh* and Gangli Gong

Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, and Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607

akghosh@purdue.edu

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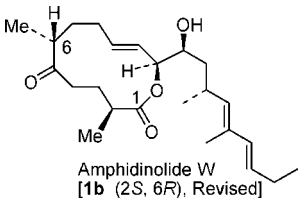

An enantioselective first total synthesis and structural revision of the cytotoxic natural product amphidinolide W is described. We initially investigated a ring-closing metathesis based synthetic strategy to form the 12-membered macrocycle. This strategy was unsuccessful as it led to formation of a 17-membered macrocycle. Subsequently, we explored an alternative strategy that involved cross-metathesis followed by a Yamaguchi macrolactonization reaction sequence utilizing the same key intermediates. This strategy led to the synthesis of amphidinolide W. The synthesis was carried out in a convergent manner, and four of the five stereogenic centers in amphidinolide W were set by asymmetric synthesis. The synthesis features Sharpless asymmetric dihydroxylation, diastereoselective alkylation, efficient cross-metathesis of functionalized substrates, and novel functional group transformations using selective lipase-catalyzed hydrolysis of the primary acetate group. Of particular note, the C6 absolute stereochemistry of amphidinolide W has now been revised through our synthesis.

Introduction

Amphidinolides are a group of structurally unique macrolides obtained from marine dinoflagellates of the genus *Amphidinium*, which are symbionts of Okinawan marine acoel flatworms *Amphiscolops* sp.[1] Amphidinolides are extremely scarce, and as a result, subsequent biological studies have been very limited. In many cases, progress toward complete structural assignments has been hampered because of lack of supply.[2] The mechanisms of action of amphidinolides have not been established due to its scarce natural abundance. The unique structural features, structural resemblence among members of the family, and potent antitumor properties have generated considerable interest in their synthesis.[3−5] Amphidinolide W (**1b**, Figure 1) was isolated by Kobayashi in 2002 from strain Y-42 of the genus *Amphidinium* dinoflagellate.[6] It is a new cytotoxic 12-membered macrolide.

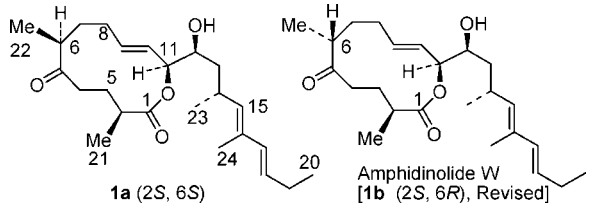

FIGURE 1. Amphidinolide W: proposed structure **1a** and revised structure **1b**.

* Corresponding author. Phone: 765-494-5323. Fax: 765-496-1612.

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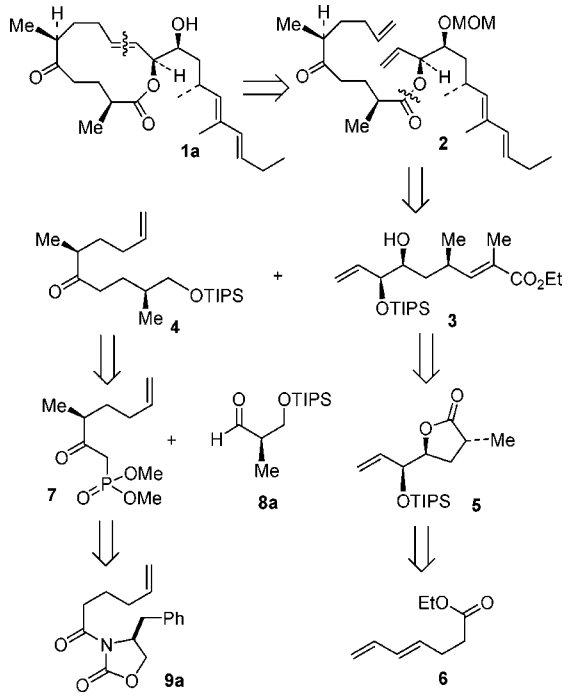


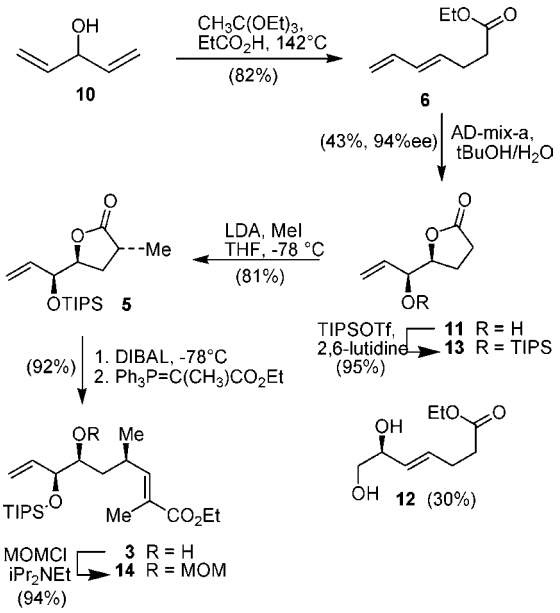
FIGURE 2. Retrosynthesis of proposed amphidinolide W (**1a**) via RCM-based strategy.

Kobayashi and co-workers elucidated the gross structure of **1a** on the basis of the spectroscopic data including $^{13}C-^{13}C$ correlation studies. The absolute configurations at C11, C12, and C14 of **1a** were assigned by *J*-based configuration analysis of a modified Mosher ester. The configurations at C2 and C6 were elucidated from NMR data of MTPA esters of a reduction product of amphidinolide W. Amphidinolide W exhibited cytotoxicity against murine lymphoma L1210 cells in vitro with an IC_{50} value of 3.9 μg/mL.[6] Recently, we reported the first total synthesis of amphidinolide W and revised the C6 absolute stereochemistry of the proposed amphidinolide W structure (**1a**).[7] We employed a combination of synthesis and NMR spectroscopy as tools to determine the correct structure of natural amphidinolide W (**1b**). Herein, we provide a complete account of our synthetic studies.

Results and Discussion

Our initial synthetic plan is outlined in Figure 2. Strategic disconnection of the proposed amphidinolide W (**1a**) at the C9−C10 double bond and a choice of the C12-MOM protecting group provide the appropriate precursor **2** for the synthesis of proposed amphidinolide W structure **1a**. We planned to assemble amphidinolide W by ring-closing metathesis followed by removal of the C12-MOM protecting group. The acyclic ester precursor **2** could be derived from esterification of an appropriately functionalized alcohol derived from intermediates **3** and an acid derived from **4**. We elected to install the C15−C18 diene functionality prior to macrocyclization. The synthons **3** and **4** can also be utilized for our alternative synthetic strategy in which the C9−C10 double bond will be introduced first by a cross-metathesis reaction followed by an appropriate macrocyclization reaction to form the 12-membered macrolactone ring for **1a**. The *syn*-diol functionality along with the trisubstituted *E*-olefin would be derived from optically active lactone **5**. The *syn*-diol stereochemistry was planned to be introduced by Sharpless asymmetric dihydroxylation[8] of readily available dienoate **6**. The subunit **4** would be prepared by a Horner−Wadsworth−Emmons reaction[9] between ketophosphonate **7** and aldehyde **8a**. Phosphonate **7** was planned to be derived from diastereoselective methylation of the acyl oxazolidinone **9a**.[10]

SCHEME 1. Synthesis of Enoate 14



Ring-Closing Metathesis-Based Strategy. As shown in Scheme 1, synthesis of C10−C17 fragment **3** started with an ortho ester Claisen rearrangement of penta-1,4-dienol **10** using triethyl orthoacetate to provide ethyl (*E*)-hepta-4,6-dienoate **6**.[11] Sharpless asymmetric dihydroxylation[8] of **6** furnished the γ-lactone **11** in 43% yield along with the other regioisomer **12**, which was obtained in 30% yield.[12] Both of these isomers were readily separated by silica gel chromatography. Mosher ester anlysis of lactone **11** revealed the enantiomeric purity of **11** to be 94% ee.[13] Protection of alcohol **11** using TIPSOTf gave the silyl ether **13**. Methylation of the lactone **13** resulted in methylated product **5** as a major diastereomer (ratio 11:1). The diastereomers were readily separated by column chromatography and the major *trans*-lactone **5** was isolated in 81% yield. The *trans* relationship between the two substituents on the five-membered-ring lactone **5** was confirmed by NOESY. Lactone **5** was reduced by DIBAL to the corresponding hemiacetal. Wittig reaction of the resulting hemiacetal with (carbethoxyethylidene)phosphorane provided the *E*-trisubstituted olefin **3** as a single isomer in 92% yield for two steps. The resulting

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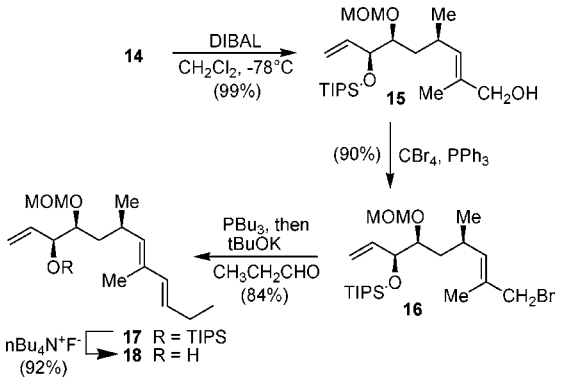
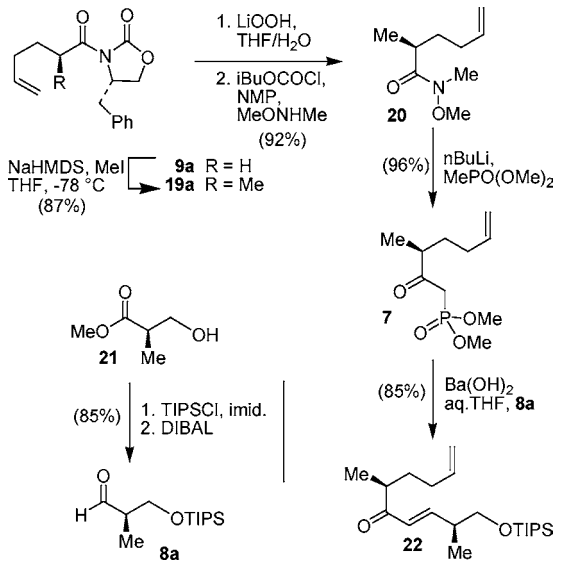
(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

SCHEME 2. Synthesis of Triene 18



SCHEME 3. Synthesis of Enone 22

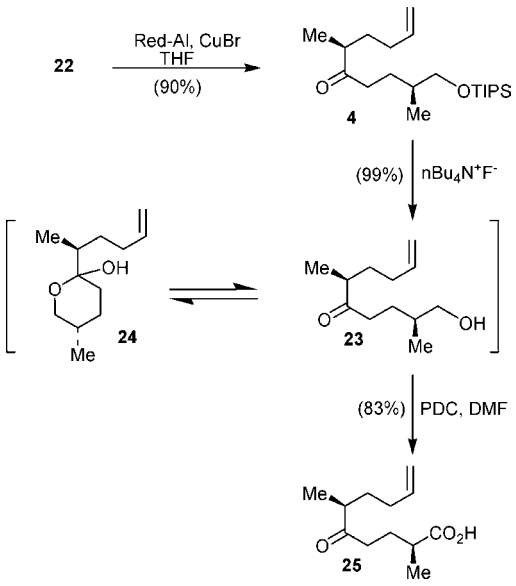


alcohol was then protected as MOM ether to afford **14** in 94% yield.

Introduction of the C15−C18-conjugated diene functionality was carried out as shown in Scheme 2. DIBAL reduction of ester **14** afforded alcohol **15**. It was converted to allylic bromide **16** by exposure to triphenylphosphine and carbon tetrabromide.[14] Reaction of bromide **16** with tributylphosphine provided the corresponding phosphonium salt. Treatment of this salt with tBuOK formed the corresponding ylid. Reaction of the resulting ylid with propionaldehyde furnished the conjugated olefin **17**. Only *E*-olefin **17** was isolated, in 75% yield for three steps (from **15**). Removal of the TIPS protecting group provided the alcohol **18**.

Synthesis of the C1−C9 fragment **5** is outlined in Scheme 3. Diastereoselective methylation of known imide **9a**[15] with NaHMDS and MeI afforded **19a** as the major diastereomer in 87% yield (ratio 15:1 by ^{1}H NMR). Evans and co-workers have previously demonstrated the stereochemical outcome of such diastereoselective alkylation process.[10] Hydrolysis of **19a** with lithium hydroperoxide provided the corresponding acid in quantitative yield. The resulting acid was converted to Weinreb amide **20** in 92% yield.[16] Addition of the lithiated dimethyl

SCHEME 4. Synthesis of Acid 25



methylphosphonate to the amide **20** at −78 °C afforded ketophosphonate **7** in excellent yield. For preparation of aldehyde **8a**, commercial methyl (*R*)-3-hydroxy-2-methylpropionate **21** was protected as the TIPS ether. DIBAL reduction of the resulting ester provided aldehyde **8a**.[17] The Horner−Wadsworth−Emmons reaction between ketophosphonate **7** and aldehyde **8a** using barium hydroxide as the base furnished α,*β*-unsaturated enone **22** without any epimerization.[18]

Enone **22** was converted to acid **25** as shown in Scheme 4. Selective conjugated reduction of enone **22** using a Red-Al and CuBr complex at −20 °C provided 1,4-reduction product **4** in 90% yield along with 5% of the 1,2-reduction byproduct.[19] This byproduct was readily separated by silica gel chromatography. Deprotection of the TIPS ether in **4** with TBAF furnished primary alcohol **23** and hemiketal **24** as a mixture. Exposure of this mixture to PDC in DMF afforded keto acid **25** in 83% isolated yield.

With both acid **25** and alcohol **18** in hand, we investigated the esterification and subsequent ring-closing metathesis strategy. As shown in Scheme 5, esterification of alcohol **18** and acid **25** in the presence of DCC and DMAP gave the ester **2**. We then examined ring-closing metathesis,[20] and the results are summarized in Table 1. As can be seen, there was no reaction when the first generation Grubbs' catalyst (**26**) was utilized (entry 1). Addition of Lewis acid $Ti(OiPr)_4$ with catalyst **26** provided the 17-membered ring macrolactone **28** in 60% yield (entry 2).[21] Furthermore, the second-generation Grubbs' catalyst (**27**)[22] provided the same 17-membered ring macrolactone **28**

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(22) Scholl, M.; Ding, S.; Lee, C.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

SCHEME 5. Ring-Closing Metathesis of 2

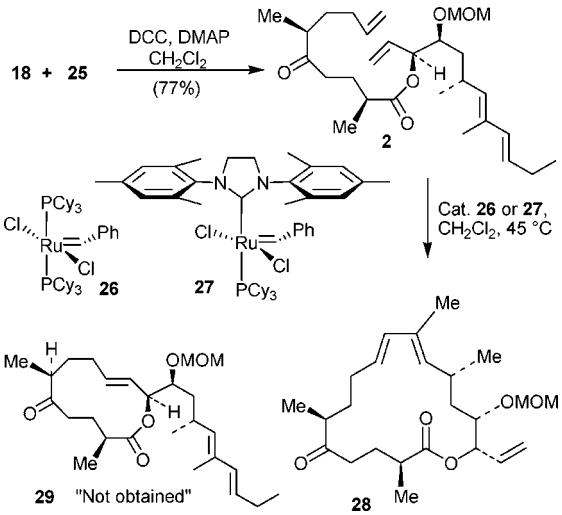


TABLE 1. RCM Strategy Study

entry	catalyst	additive	product (yield, %)
1	**26**	no	no reaction
2	**26**	$Ti(O^iPr)_4$	**28** (60)
3	**27**	no	**28** (82)

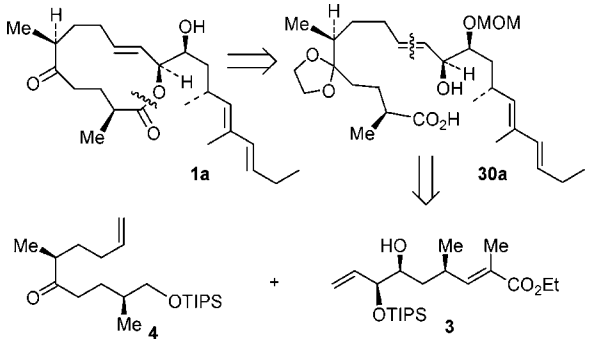
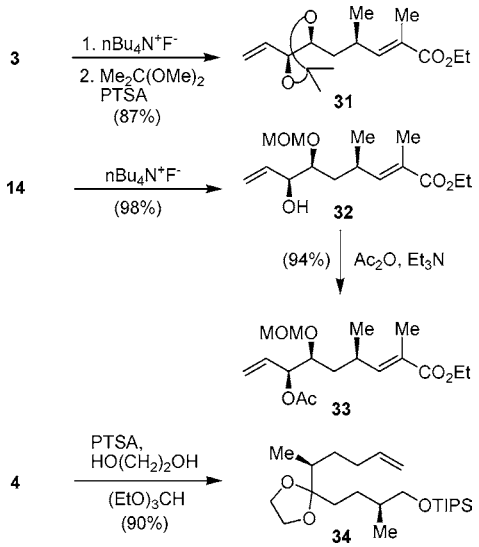


FIGURE 3. Retrosynthesis of **1a** via macrolactonization-based strategy.

in 82% yield (entry 3). No desired 12-membered ring lactone **29** resulting from ring-closing metathesis of terminal olefins was obtained. Formation of the 17-membered ring is definitely more favorable than the 12-membered ring due to both enthalpic and entropic reasons.[20e] It is possible to form a 12-membered macrolactone involving a methathesis substrate that lacks the C15−C18 diene functionality. However, in our synthetic strategy, we planned to avoid installation of this functionality at a late stage of the synthesis. Therefore, we elected to explore an alternative strategy utilizing the same synthons **3** and **4**.

Cross-Metathesis and Macrolactonization-Based Strategy. We then turned to a cross-metathesis[23] and macrolactonization sequence for assembly of the macrolide **1a**. As shown in Figure 3, we planned to form the 12-membered macrolactone by Yamaguchi macrolactonization[24] of acyclic seco acid **30a**. The C9−C10 *trans*-olefin in this seco acid would be installed by

SCHEME 6. Preparation of the Substrates for Cross-Metathesis



cross-metathesis of substrates derived from **3** and **4**. The second-generation Grubbs' catalyst **27** is generally superior to first-generation **26** for the cross-metathesis reactions.[23] However, we found that the conjugated diene in **2** was vulnerable to the second-generation Grubbs' catalyst in the ring-closing metathesis reaction, which led to the formation of 17-membered macrolactone **28** in excellent yield. Therefore, we elected to modify our substrate for the cross-metathesis. Since the trisubstituted internal olefin in α,β-unsaturated ester **3** is much more inert toward the second-generation Grubbs' catalyst for steric and electronic reasons, one can expect the cross-metathesis reaction involving electron-rich monosubstituted terminal olefins in **3** and **4** will proceed preferentially.

However, the choice of the protecting group in substrate **3** may be critical to yields and olefin geometry. We, therefore, planned to investigate cross-metathesis involving enoate **3** and its derivatives (**31**−**33**) with different protecting groups. Preparation of various substrates for cross-metathesis is outlined in Scheme 6. Removal of the TIPS in **3** followed by protecting the diol as the acetonide gave **31**. Removal of the TIPS in **14** provided alcohol **32**. Protection of **32** with acetic anhydride and triethylamine provided acetate **33**. We planned to protect the ketone in **4** as its dioxolane derivative and examine cross metathesis with this substrate. Thus, **4** was reacted with ethylene glycol and triethyl orthoformate in the presence of PTSA to give dioxolane **34** in 90% yield.[25]

As shown in Scheme 7, using olefin **34** and a range of C10−C17 enoates (**3**, **31**−**33**) in hand, we investigated cross-metathesis reactions under a variety of reaction conditions, and the results are shown in Table 2. Cross-metathesis of **3** and **34** provided diene **35** with a very good *E*/*Z* ratio of 10:1; however, the reaction yield (25%) was far from satisfactory (entry 1). The presence of the bulky allylic TIPS group in **3** may have been the reason for this inefficient reaction. To examine the effect of a hydroxyl group or other protecting group, we removed the TIPS group in **3** to provide the alcohol **32**. However, no cross-metathesis product was obtained between

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SCHEME 7. Cross-Metathesis Reactions of Various Substrates

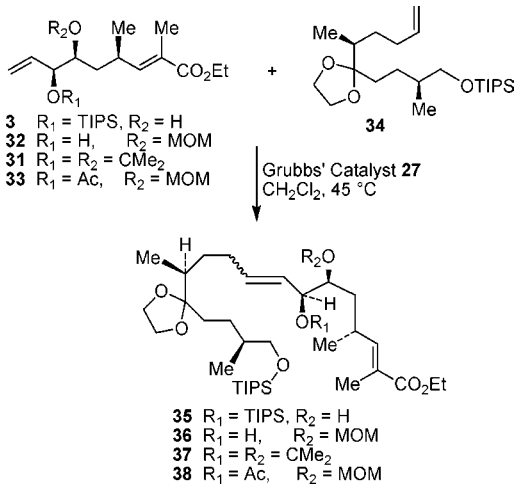


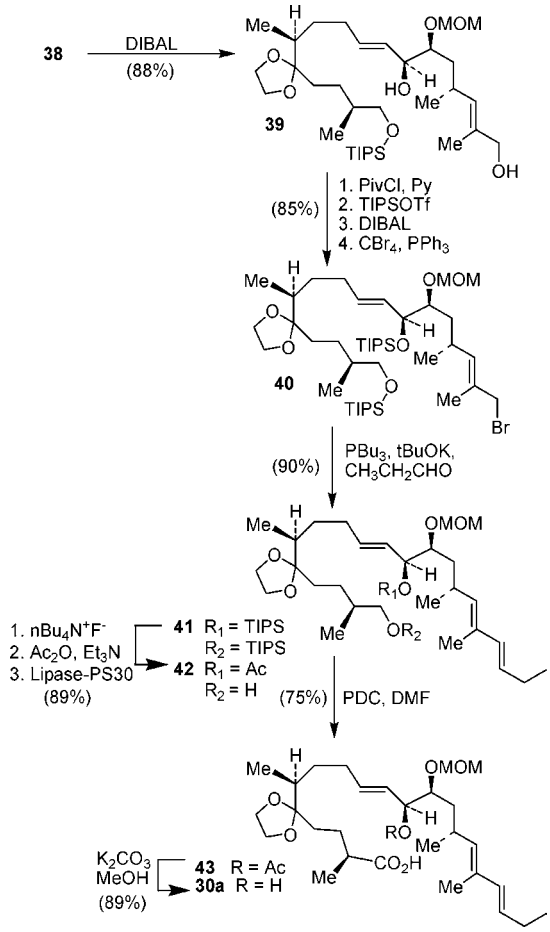
TABLE 2. Results of Cross Metathesis Studies

entry	olefins	product	yield (%)	*E*/*Z*
1	**3** + **34**	**35**	25	10:1
2	**32** + **34**	**36**	0	N/A
3	**31** + **34**	**37**	73	2:1
4	**33** + **34**	**38**	86	11:1

32 and **34** (entry 2). Allylic alcohol in **32** may have sequestered the Ru−carbene complex through strong chelation with the hydroxyl group. Appropriate protection of the allylic alcohol was deemed necessary for effective cross-metathesis reaction. Cross-metathesis of isopropylidene derivative **31** and dioxolane **34** proceeded with good yield; however, the *E*/*Z* selectivity was only 2:1 (entry 3). To improve the *E*/*Z* ratio, acetyl and MOM groups in **33** were investigated. As shown, cross-metathesis of **33** and **34** provided product **38** in excellent yield (86%) and very good *E*/*Z* selectivity (up to 11:1). The *E*/*Z* mixture could not be separated by silica gel chromatography. Therefore, the mixture was used for the subsequent reaction.

With the optimized cross-metathesis product **38** in hand, we then focused on the synthesis of seco acid **30a** (Figure 3) for macrolactonization. As shown in Scheme 8, reduction of **38** by DIBAL afforded the readily separable *E*-diol **39** in 88% yield. It was converted to allylic bromide **40** in a four step sequence involving the following: (1) regioselective protection of the primary alcohol with pivaloyl chloride and pyridine; (2) protection of the secondary alcohol with TIPSOTf; (3) deprotection of the pivalate with DIBAL; (4) conversion of the resulting allylic alcohol to bromide **40** with carbon tetrabromide and triphenylphosphine.[14] Bromide **40** was isolated in 85% overall yield. Reaction of this bromide with tributylphosphine provided the corresponding tributylphosphonium salt. Wittig olefination of this salt with propionaldehyde in the presence of KOtBu in THF/Benzene provided exclusively *E*-olefin **41** in 90% yield. Selective removal of the primary TIPS group was unsuccessful. Therefore, both TIPS groups were removed using TBAF to furnish the corresponding diol. Protection of the diol with acetic anhydride and triethylamine afforded the corresponding diacetate. Selective basic hydrolysis of the primary acetate was attempted using LiOH, $Ba(OH)_2$, or aqueous KCN. None of the conditions was effective as both acetates were hydrolyzed under the reaction conditions. However, lipase PS-30 catalyzed hydrolysis of the diacetate proceeded very selectively providing the primary alcohol **42** in excellent yield (89% over three steps).[26] Oxidation of alcohol **42** with PDC in DMF furnished the corresponding acid **43**. Saponification of the secondary acetate group with K_2CO_3 in MeOH furnished seco acid **30a** in 67% yield over two steps.

SCHEME 8. Synthesis of Seco Acid 30a



Synthesis of the Proposed Structure of Amphidinolide W (1a). With seco acid **30a** in hand, we then proceeded to form the 12-membered macrolactone. As shown in Scheme 9, Yamaguchi macrolactonizaion[24] of **30a** afforded two diastereomeric macrolactones **44a** and **44c** as a 3:1 mixture. Presumably, these lactones were formed due to base-catalyzed epimerization of the C2 stereogenic center during the reaction. Our many attempts to prevent this epimerization under different macrolactonization conditions including DCC/DMAP as reported by Borden and Keck[27] as well as acid-catalyzed macrolactonization protocol reported by Trost and Chisholm[28] were unsuccessful. The isomers were readily separated by silica gel chromatography. Treatment of the major isomer **44a** with PPTS in aqueous acetone removed the dioxolane group. Subsequent removal of the MOM group with $BF_3{\cdot}OEt_2$ furnished the presumed natural amphidinolide W (**1a**). However, ^1H and ^{13}C NMR spectra for **1a** did not match with those reported for natural amphidinolide

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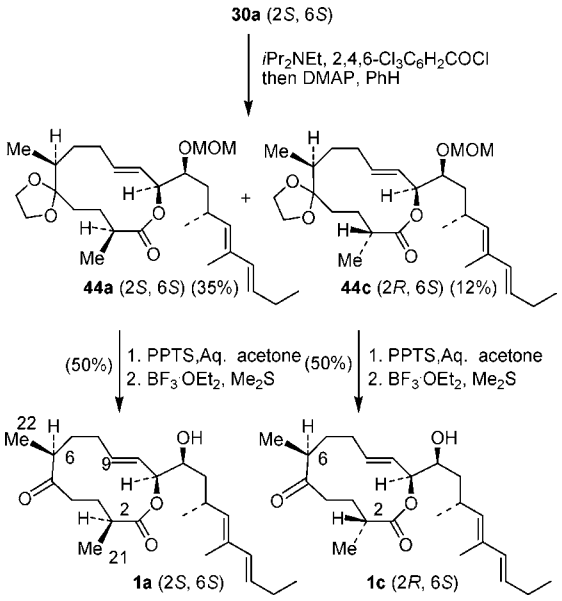
(28) Trost, B. M.; Chisholm, J. D. *Org. Lett*. **2002**, *4*, 3743.

SCHEME 9. Synthesis of Proposed Amphidinolide W (1a)

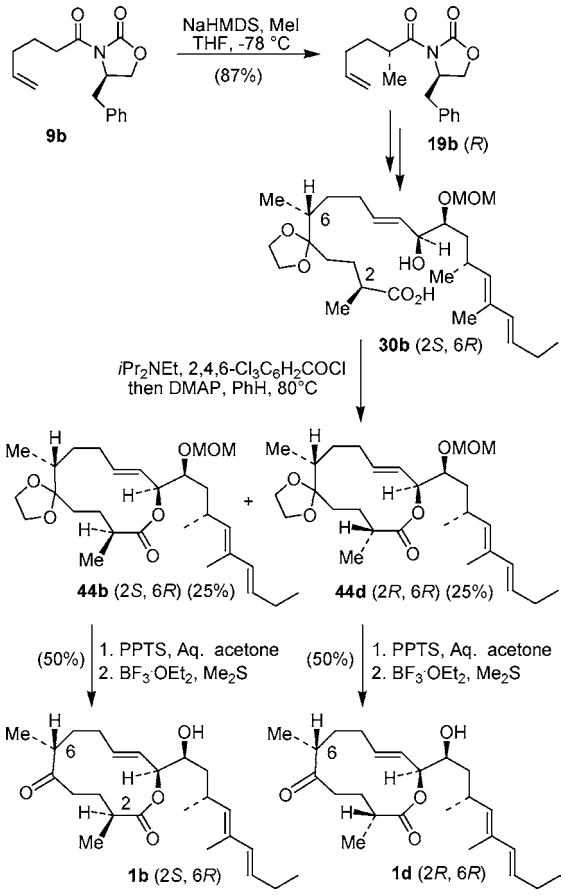


W. Furthermore, deprotection of both dioxolane and MOM groups from the minor isomer **44c** afforded amphidinolide W diastereomer **1c**. Unfortunately, neither ^{1}H nor ^{13}C NMR spectra for **1c** were identical with those of the natural product.[6] It should be noted that removal of dioxolane and MOM protecting groups proceeded in 50% yield in a two-step sequence, and no epimerization was observed under the reaction conditions.

Structural Revision of Amphidinolide W. A thorough examination of ^{1}H and ^{13}C NMR spectra of **1a** and **1c** and comparison of reported spectra[6] for natural amphidinolide W revealed that the discrepancies of chemical shifts are mostly located in the ring instead of the side chain. The ^{1}H and ^{13}C NMR chemical shifts of the C12−C20 side-chain region of isomers **1a** and **1c** matched very closely with the reported values of the natural amphidinolide W. However, there were significant discrepancies of chemical shifts in the C2−C11 ring region, particularly ^{1}H NMR chemical shifts at C2−C8 and the ^{13}C NMR chemical shifts at C2, C4, C5, C9, and C11.[6] The actual structure of amphidinolide W appeared to be epimeric to the proposed structure at one or more stereocenters in the ring system. The 2*S*-configuration of natural amphidinolide W was deduced from NMR data of 1,5,11,12-tetrakis-MTPA esters of a reductive product of amphidinolide W.[6] The absolute stereochemistry at C6 was elucidated to be the *S* configuration on the basis of NMR data of 6,11,12-tris-MTPA esters of the C6−C20 segment obtained by the Baeyer−Villiger reaction of amphidinolide W.[6] Among all the stereocenters, the C2 and C6 configuration assignments were more liable to error since neither of the stereocenters is in close proximity to other stereocenters. As a consequence, no stereochemical correlation could be posited to conclusively assign the relative and absolute stereochemistry. Since we had already prepared both C2 epimers (**1a** and **1c**) and neither of them corresponded to natural amphidinolide W, we hypothesized that the C6 stereocenter of originally proposed amphidinolide W structure may require revision.

Thus, we turned to synthesis of the C6-epimer (*R*-configuration) of the originally proposed structure of amphidinolide W (**1a**). Our attempted direct epimerization of C6 stereocenter using a variety of conditions (KOtBu in THF at 0 °C; KH in THF at 0 °C; DBU in CH_2Cl_2 or in MeOH) resulted in the decomposition of the starting material. While it is possible to epimerize the C-6 stereocenter in **5**, we elected to synthesize 6-*R*-stereoisomer diastereoselectively to avoid any ambiguity. Therefore, for introduction of *R*-stereochemistry at C6, diastereoselective methylation was carried out with oxazolidinone derivative **9b** (enantiomer of **9a)**. Stereochemical outcome of such alkylation process is now well established.[10] As shown in Scheme 10, deprotonation of **9b** with NaHMDS followed by alkylation with MeI afforded **19b** as the major diastereomer in 87% yield (ratio 12:1 by ^{1}H NMR). The alkylated oxazolidinone derivative **19b** was converted to seco acid **30b** following the reactions sequence described for **30a**. Yamaguchi macrolactonization[24] of seco acid **30b** as described previously furnished two diastereomeric macrolactones, **44b** and **44d**, as a mixture (1:1 ratio) in 50% yield. Both isomers were separated by silica gel chromatography. Our many attempts to improve this ratio were unsuccessful. Removal of dioxolane and MOM protecting groups from diastereomer **44b** provided synthetic amphidinolide W (**1b**) in 50% yield for two steps. The spectral data (^{1}H and ^{13}C NMR) for **1b** ($[\alpha]^{23}_D$ +8.1, *c* 1, $CHCl_3$)[7] were identical with those reported for the natural amphinolide W.[6] Deprotection of dioxolane and MOM protecting groups of diastereomer **44d** furnished the C2 diastereomer of amphidinolide W (**1d**). The stereochemical identifications at the C2 positions of **1b** and **1d** were established by NOESY as shown in Figure 4. A significant NOE effect was observed between H_A and H_B protons in **1b**. On the other hand, there was no observable NOE between H_A and H_B protons in **1d**.

SCHEME 10. Synthesis of Amphidinolide W (1b) and Its Isomer 1d



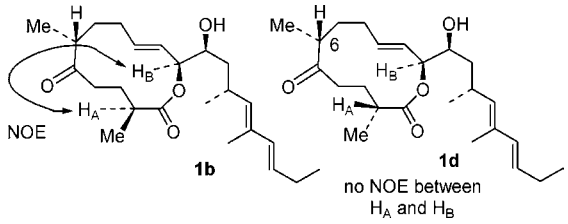
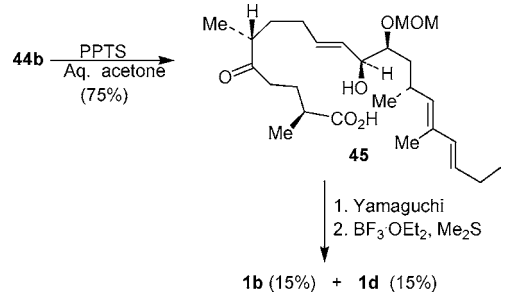
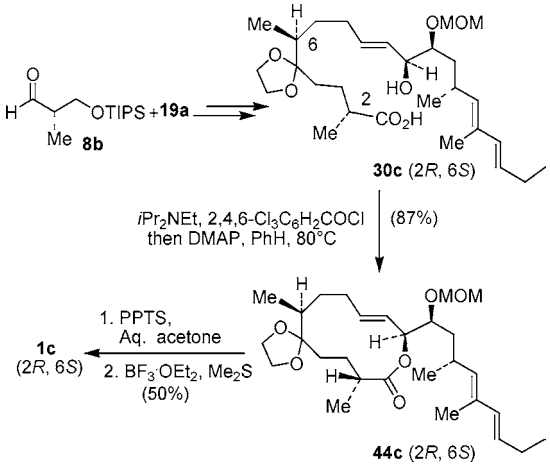


FIGURE 4. NOE effect of diastereomes **1b** and **1d**.

SCHEME 11. Effect of Dioxolane on Macrocyclization



SCHEME 12. Enantioselective Synthesis of Diastereomer 1c

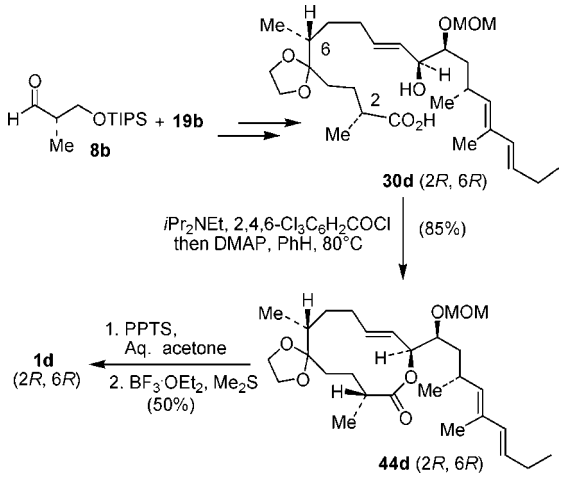


We then examined the effect of the dioxolane protecting group on macrolactonization. As shown in Scheme 11, treatment of **44b** with PPTS in aqueous acetone resulted in the removal of the dioxolane group. The resulting keto seco acid **45** was subjected to Yamaguchi macrolactonization. This condition also provided a 1:1 mixture of macrolactones. Removal of the MOM group by exposure to $BF_3{\cdot}OEt_2$ and Me_2S afforded **1b** and **1d** in 30% yield for two steps. Therefore, it is evident that the dioxolane ring on **44b** did not play any role for epimerization of the C2 stereogenic center during the macrocyclization.

To further confirm the C2 stereochemistry of amphidinolide W diastereomers **1c** and **1d**, we synthesized the corresponding enantiomerically pure seco acids and investigated Yamaguchi macrolactonization. As shown in Scheme 12, following the same procedures for the synthesis of **30a**, enantiomeric aldehyde **8b** was converted to enantiomerically pure seco acid **30c**. Interestingly, cyclization of **30c** under the same Yamaguchi condition furnished a single macrolactone **44c** in excellent yield. There was no epimerizaion at C2. Further deprotection of dioxolane and MOM groups furnished **1c** as a single isomer.

As shown in Scheme 13, we also synthesized **1d** from the corresponding seco acid **30d**. Thus, enantiomeric aldehyde **8b** and acyl oxazolidinone **19b** were converted to enantiomerically

SCHEME 13. Enantioselective Synthesis of Diastereomer 1d



pure seco acid **30d** as described above. Yamaguchi macrolactonization of **30d** afforded a single macrolactone **44d** in 85% yield. There was no epimerization at the C2 stereogenic center. Removal of dioxolane and MOM protecting groups from macrolactone **44d** afforded **1d** as a single isomer. These experiments further provided evidence in support of the assignment of C2 and C6 absolute stereochemistry of amphidinolide W structure **1b**.

Conclusion

In summary, we have achieved the first total synthesis of amphidinolide W (**1b**) along with three diastereomers (**1a**, **1c**, **1d**), thus leading to a revision of the structure **1a** originally proposed for natural amphidinolide W. The convergent synthesis features Sharpless asymmetric dihydroxylation, diastereoselective alkylation, efficient cross metathesis of functionalized substrates, and novel functional group transformations using selective lipase-catalyzed hydrolysis of a primary acetate group. Of particular note, the C6 absolute stereochemistry of amphidinolide W (**1b**) has now been revised through our synthesis. Also, optical rotation of amphidinolide W was reported for the first time after total synthesis. It is important to note that amphidinolide W and its diastereomers are very unstable and prone to decomposition even when they were stored at low temperature.

Experimental Section

(2*S*,6*S*)-((3*S*,4*S*,6*R*,7*E*,9*E*)-4-(Methoxymethoxy)-6,8-dimethyldodeca-1,7,9-trien-3-yl)-2,6-dimethyl-5-oxodec-9-enoate (2). To a solution of alcohol **18** (137 mg, 0.51 mmol) and acid **25** (110 mg, 0.52 mg) in CH_2Cl_2 (4 mL) was added DCC (118 mg, 0.57 mmol) followed by DMAP (7 mg, 0.05 mmol). The mixture was stirred at room temperature overnight, filtered, and concentrated in vacuo. Purification by flash column (5% EtOAc/hexanes) afforded ester **2** (182 mg, 77%) as a clear oil: $[\alpha]^{23}_D$ −5.3 (*c* 1.25, $CHCl_3$); IR (neat) 1736, 1714, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (d, J = 16.0 Hz, 1H), 5.86 (ddd, J = 17.0, 11.0, 6.0 Hz, 1H), 5.75 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H), 5.59 (dt, J = 15.5, 6.5 Hz, 1H), 5.39 (dd, J = 6.0, 5.0 Hz, 1H), 5.28 (d, J = 17.5 Hz, 1H), 5.26 (d, J = 11.0 Hz, 1H), 5.05 (d, J = 9.5 Hz, 1H), 5.00 (d, J = 17.0 Hz, 1H), 4.96 (d, J = 10.0 Hz, 1H), 4.64 (AB, J_{AB} = 6.5 Hz, $\Delta\nu_{AB}$ = 26.0 Hz, 2H), 3.50 (m, 1H), 3.38 (s, 3H), 2.70 (m, 1H), 2.45−2.54 (m, 4H), 2.09 (m, 2H), 2.01 (m, 2H), 1.88 (m, 1H), 1.76 (m, 2H), 1.72 (s, 3H), 1.51 (m, 1H), 1.38 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 1.00 (t, J = 7.5 Hz,

3H), 0.96 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 174.9, 138.0, 135.7, 133.7, 133.3, 129.8, 118.0, 115.1, 97.5, 77.9, 75.0, 56.0, 45.6, 39.1, 38.8, 38.7, 31.9, 31.4, 28.9, 27.2, 25.9, 21.8, 17.4, 16.4, 13.9, 12.7; HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{46}O_5Na$ 485.3243, found 485.3267.

RCM Product (28). To a solution of **2** (25 mg, 0.054 mmol) in DCM (27 mL) was added second-generation Grubbs' catalyst **27** (4.6 mg, 0.0054 mmol). The reaction was heated to 45 °C for 2 h and then cooled to room temperature. The mixture was concentrated in vacuo and purified by column chromatography (10% EtOAc/hexanes) to afford **28** (18 mg, 82%) as a clear oil: $[\alpha]^{23}_D$ +92 (*c* 1.0, $CHCl_3$); IR (neat) 1737, 1709, 1041; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (d, J = 16.0 Hz, 1H), 5.88 (ddd, J = 17.0, 10.5, 5.0 Hz, 1H), 5.49 (m, 1H), 5.30 (ddd, J = 15.0, 10.0, 5.0 Hz, 1H), 5.26 (d, J = 17.5 Hz, 1H), 5.25 (d, J = 10.0 Hz, 1H), 5.02 (d, J = 10.0 Hz, 1H), 4.74 (AB, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 34.5 Hz, 2H), 3.42 (s, 3H), 3.34 (m, 1H), 2.59 (m, 1H), 2.48 (m, 1H), 2.32−2.39 (m, 3H), 2.16 (m, 1H), 1.93 (m, 2H), 1.76 (m, 1H), 1.67 (s, 3H), 1.58 (m, 1H), 1.49 (m, 1H), 1.38 (m, 2H), 1.13 (d, J = 6.5 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 175.4, 137.0, 135.8, 132.2, 131.9, 128.5, 117.4, 96.8, 78.2, 73.4, 55.9, 46.1, 42.0, 39.2, 39.1, 33.3, 32.8, 29.4, 29.0, 22.3, 18.8, 17.0, 13.0; HRMS (ESI) $[M + Na]^+$ calcd for $C_{24}H_{38}O_5Na$ 429.2617, found 429.2614.

Cross-Metathesis Product (35). To a mixture of **34** (120 mg, 0.30 mmol) and **3** (60 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added second-generation Grubbs' catalyst **27** (7 mg, 0.008 mmol). The reaction was heated to 45 °C for 15 h and then cooled to room temperature. The mixture was concentrated in vacuo and purified by column chromatography (5−10% EtOAc/Hexanes) to afford **35** (28 mg, 25%, inseparable mixture of 10:1 *E*/*Z* isomers) as a clear oil along with the dimer of **34** (100 mg) and recovered **3** (42 mg): IR (neat) 3500, 1712, 1099; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, J = 8.5 Hz, 1H), 5.59 (dt, J = 15.5, 6.5 Hz, 1H), 5.38 (dd, J = 15.5, 8.5 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 3.87−3.93 (m, 5H), 3.44−3.54 (m, 2H), 3.22 (m, 1H), 2.89 (m, 1H), 2.17 (m, 1H), 1.97 (m, 1H), 1.88 (s, 3H), 1.37−1.72 (m, 8H), 1.29 (t, J = 7.0 Hz, 3H), 1.26 (m, 1H), 1.01−1.64, (m, 46H), 0.92 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 147.1, 134.7, 130.0, 127.4, 113.9, 78.7, 73.1, 68.6, 65.3, 60.4, 39.7, 39.4, 36.4, 31.7, 30.6, 30.4, 29.9, 29.7, 26.6, 20.9, 18.2, 18.1, 16.9, 14.3, 14.1, 12.5, 12.4, 12.0; HRMS (ESI) $[M + Na]^+$ calcd for $C_{43}H_{84}O_7Si_2Na$ 791.5654, found 791.5660.

Cross-Metathesis Product (36). To a mixture of **34** (127 mg, 0.32 mmol) and **31** (45 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was added second-generation Grubbs' catalyst **27** (8 mg, 0.009 mmol). The reaction was heated to 45 °C for 15 h and then cooled to room temperature. The mixture was concentrated in vacuo and purified by column chromatography (5−10% EtOAc/hexanes) to afford **36** (76 mg, 73%, inseparable mixture of 2:1 *E*/*Z* isomers) as a clear oil along with the dimer of **34** (79 mg): IR (neat) 1712, 1462, 1106; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (m, 1H), 5.66−5.77 (m, 1H), 5.35 (m, 1H), 4.18 (m, 2H), 3.83−3.91 (m, 5H), 3.43−3.53 (m, 3H), 2.80 (m, 1H), 1.94−2.38 (m, 2H), 1.85 (s, 3H), 1.50−1.70 (m, 8H), 1.39 (s, 3H), 1.36 (s, 3H), 1.29 (m, 3H), 1.01−1.15 (m, 26H), 0.89−0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer δ 168.4, 146.4, 137.1, 127.5, 126.4, 113.9, 108.1, 82.9, 78.4, 68.6, 65.3, 65.2, 60.5, 39.5, 38.5, 36.3, 31.5, 30.7, 30.6, 30.4, 27.4, 26.9, 26.6, 20.7, 18.1, 16.9, 14.3, 14.2, 12.5, 12.0; HRMS (ESI) $[M + Na]^+$ calcd for $C_{37}H_{68}O_7SiNa$ 675.4632, found 675.4628.

Cross-Metathesis Product (38). To a mixture of **34** (369 mg, 0.927 mmol) and **33** (145 mg, 0.442 mmol) in CH_2Cl_2 (1 mL) was added second-generation Grubbs' catalyst **27** (34 mg, 0.04 mmol). The reaction was heated to 45 °C for 15 h and then cooled to room temperature. The mixture was concentrated in vacuo and purified by column chromatography (15% EtOAc/hexanes) to afford **38** (262 mg, 85%, inseparable mixture of 11:1 *E*/*Z* isomers) as a clear oil along with the dimer of **34** (191 mg): IR (neat) 1742, 1711; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, J = 10.1 Hz, 1H), 5.74 (dt, J = 15.4, 6.5 Hz, 1H), 5.43 (dd, J = 15.4, 7.1 Hz, 1H), 5.31 (dd, J = 6.4, 5.4 Hz, 1H), 4.63 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.91 (m, 4H), 3.43−3.52 (m, 3H), 3.37 (s, 3H), 2.72 (m, 1H), 2.17 (m, 1H), 2.05 (s, 3H), 1.97 (m, 1H), 1.83 (s, 3H), 1.50−1.70 (m, 8H), 1.29 (t, J = 7.2 Hz, 3H), 1.24 (m, 1H), 1.08 (m, 1H), 1.04, (m, 21H), 1.01 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 168.6, 147.2, 136.5, 127.8, 124.7, 114.3, 97.6, 78.5, 75.8, 69.0, 68.9, 65.6, 65.5, 60.9, 56.3, 39.7, 38.6, 36.7, 31.8, 31.1, 30.7, 30.1, 26.9, 21.6, 20.9, 18.5, 17.3, 14.7, 14.5, 12.9, 12.4; HRMS (ESI) $[M + Na]^+$ calcd for $C_{38}H_{70}O_9SiNa$ 721.4687, found 721.4673.

Macrolactone (44a). To a solution of hydroxy acid **30a** (23 mg, 0.046 mmol) in THF (2 mL) were added diisopropylethylamine (0.32 mL, 1.85 mmol) and 2,4,6-trichlorobenzoyl chloride (0.14 mL, 0.93 mmol). The reaction was stirred at room temperature overnight. The mixture was diluted by addition of benzene (8 mL) and added slowly to a solution of DMAP (283 mg, 2.3 mmol) in benzene (50 mL) at 80 °C by syringe pump over 8 h. The syringe was rinsed with benzene (2 mL), and the solution was combined to the reaction mixture to stir for an additional 1 h. After being cooled to room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution, and the aqueous solution was extracted with EtOAc twice. The combined organic layers were washed with pH 4 buffer (aqueous solution of NaH_2PO_4 + $NaHSO_4$), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column (15% EtOAc/Hexanes) afforded the macrolactone **44a** (7.5 mg, 35%) as a clear oil along with the diastereomer **44c** (2.5 mg, 12%): IR (neat) 1720; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (dt, J = 16.0, 7.2 Hz, 1H), 6.04 (d, J = 15.4 Hz, 1H), 5.64 (dt, J = 15.8, 7.0 Hz, 1H), 5.61 (dd, J = 15.4, 6.4 Hz, 1H), 5.15 (dd, J = 8.1, 7.8 Hz, 1H), 5.09 (d, J = 9.2 Hz, 1H), 4.66 (d, J = 6.6 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 3.88 (m, 4H), 3.72 (m, 1H), 3.36 (s, 3H), 2.74 (m, 1H), 2.62 (m, 1H), 2.12 (m, 3H), 1.92 (m, 1H), 1.75 (s, 3H), 1.50−1.76 (m, 5H), 1.43 (m, 2H), 1.34 (m, 1H), 1.26 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 140.1, 136.3, 134.2, 133.7, 130.1, 128.7, 113.2, 97.9, 78.3, 78.0, 65.7, 65.0, 56.2, 40.4, 39.6, 36.7, 35.7, 30.0, 29.4, 28.9, 27.2, 26.3, 22.2, 14.3, 14.1, 13.8, 13.1; HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{46}O_6Na$ 501.3192, found 501.3193.

Proposed Amphidinolide W (1a). To a solution of macrolactone **44a** (7.5 mg, 0.016 mmol) in acetone/H_2O (3 mL/0.2 mL) was added PPTS (79 mg, 0.31 mmol). The mixture was heated to 40 °C and stirred overnight. After being cooled to room temperature, the mixture was poured into H_2O and extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification on silica gel (15% EtOAc/hexanes) provided ketolactone (5.9 mg, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (d, J = 15.7 Hz, 1H), 5.64 (dt, J = 15.6, 6.5 Hz, 1H), 5.56 (dt, J = 15.7, 6.9 Hz, 1H), 5.46 (dd, J = 15.6, 7.4 Hz, 1H), 5.11 (dd, J = 7.4, 7.2 Hz, 1H), 5.02 (d, J = 9.6 Hz, 1H), 4.66 (d, J = 6.5 Hz, 1H), 4.59 (d, J = 6.6 Hz, 1H), 3.51 (m, 1H), 3.36 (s, 3H), 2.71 (m, 1H), 2.41−2.50 (m, 4H), 2.25 (m, 1H), 2.12 (m, 2H), 2.08 (m, 2H), 1.93 (m, 1H), 1.74 (s, 3H), 1.61 (m, 1H), 1.44 (m, 1H), 1.38 (m, 1H), 1.25 (m, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 1.03 (t, J = 7.5 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 175.4, 137.0, 136.2, 134.2, 133.7, 130.1, 128.0, 98.0, 78.2, 75.7, 56.2, 45.6, 41.7, 40.0, 39.1, 32.5, 30.1, 29.5, 27.3, 26.3, 22.2, 18.1, 17.5, 14.3, 13.1.

To a solution of above product (5.9 mg, 0.01 mmol) in CH_2Cl_2 (2 mL) was added dimethyl sulfide (1 mL) followed by $BF_3{\cdot}OEt_2$ (17 μL, 0.14 mmol) at −20 °C. After 15 min at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by preparative TLC (20% EtOAc/hexanes) provided pure **1a** (3.1 mg, 60%) as a colorless oil: $[\alpha]^{23}_D$ +27 (*c* 0.23, $CHCl_3$); IR (neat) 3468, 1729; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (d, J = 15.4 Hz, 1H), 5.64 (dt,

J = 15.6, 6.6 Hz, 1H), 5.56 (dt, J = 15.3, 6.6 Hz, 1H), 5.50 (dd, J = 15.9, 6.6 Hz, 1H), 5.01 (d, J = 9.8 Hz, 1H), 4.86 (dd, J = 7.2, 7.2 Hz, 1H), 3.60 (m, 1H), 2.84 (m, 1H), 2.45 (m, 4H), 2.24 (m, 1H), 2.13 (m, 2H), 2.01 (m, 2H), 1.92 (m, 1H), 1.78 (s, 3H), 1.68 (m, 1H), 1.39 (m, 2H), 1.28 (m, 1H), 1.19 (d, J = 6.8 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 175.3, 136.9, 135.5, 133.8, 133.5, 129.8, 127.6, 77.3, 70.5, 45.4, 41.3, 40.4, 38.6, 32.1, 30.2, 28.9, 26.5, 25.9, 21.8, 17.9, 17.3, 13.9, 12.7; HRMS (ESI) $[M + Na]^+$ calcd for $C_{24}H_{38}O_4Na$ 413.2668, found 413.2651.

Macrolactone (44b). According to the same procedures for preparation of **44a** from acid **30a**, acid **30b** (110 mg, 0.22 mmol) was converted to macrolactone **44b** (26 mg, 25%) as a clear oil along with the diastereomer **44d** (26 mg, 25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, J = 15.3 Hz, 1H), 5.87 (m, 1H), 5.61 (dt, J = 15.3, 6.6 Hz, 1H), 5.33−5.36 (m, 2H), 5.07 (d, J = 9.1 Hz, 1H), 4.62 (dd, J = 18.9, 6.6 Hz, 2H), 3.86 (m, 4H), 3.55 (m, 1H), 3.36 (s, 3H), 2.73 (m, 1H), 2.06−2.26 (m, 4H), 1.75 (s, 3H), 1.26−1.76 (m, 9H), 1.14 (d, J = 6.9 Hz, 3H), 1.01 (t, J = 7.8 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 138.4, 135.7, 133.5, 133.0, 129.5, 127.0, 112.1, 100.9, 97.2, 75.6, 65.0, 63.9, 55.5, 41.2, 39.3, 34.5, 31.8, 31.6, 30.2, 30.1, 28.8, 25.6, 21.5, 16.9, 13.7, 13.6, 12.4. HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{46}O_6Na$ 501.3192, found 501.3189.

Synthetic Amphidinolide W (1b). According to the same procedures for preparation of **1a** from **44a**, macrolactone **44b** (26 mg, 0.054 mmol) was converted to synthetic amphidinolide W **(1b)** (12 mg, 50% for two steps) as a clear oil: $[\alpha]^{23}_D$ +8.1 (*c* 1, $CHCl_3$); IR (neat) 3468, 1729; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (d, J = 15.7 Hz, 1H), 5.64 (dt, J = 15.4, 6.4 Hz, 1H), 5.62 (dt, J = 15.6, 6.6 Hz, 1H), 5.52 (dd, J = 15.4, 8.5 Hz, 1H), 5.04 (d, J = 9.7 Hz, 1H), 4.96 (dd, J = 8.3, 6.6 Hz, 1H), 3.56 (ddd, J = 10.0, 6.7, 2.2, 1H), 2.83 (m, 1H), 2.64 (m, 1H), 2.49 (dt, J = 18.3, 6.3 Hz, 1H), 2.38 (m, 1H), 2.34 (m, 1H), 2.31 (m, 1H), 2.17 (m, 1H), 2.11 (m, 2H), 1.89 (m, 2H), 1.77 (s, 3H), 1.65 (m, 1H), 1.50 (m, 1H), 1.41 (ddd, J = 14.0, 10.5, 3.5, 1H), 1.26 (ddd, 13.9, 11.5, 2.2, 1H), 1.15 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 175.3, 138.2, 135.5, 133.7, 133.5, 129.8, 127.2, 79.0, 70.6, 45.8, 41.0, 39.3, 35.9, 32.3, 32.3, 28.8, 26.5, 25.8, 21.7, 18.6, 16.4, 13.8, 12.7; HRMS (ESI) $[M + Na]^+$ calcd for $C_{24}H_{38}O_4Na$ 413.2668, found 413.2662.

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Supporting Information Available: Full experimental details and characterization; copies of ^{1}H and ^{13}C NMR spectra of selected compounds; tables of comparison of the NMR data of synthetic amphidinolide W (**1b**) and its isomers **1a**, **1c**, and **1d** with those reported in the literature. This material is available free of charge via the Internet at http://pubs.acs.org.

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