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Total Synthesis and Structural Revision of (+)-Amphidinolide W

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Amphidinolides are a family of cytotoxic macrolides with significant antitumor properties.[1] However, the natural abundance of amphidinolides is very limited and as a consequence, biological studies have been severely hampered. Amphidinolide W, a novel 12-membered macrolide, has been recently isolated from the marine dinoflagellate *Amphidinolide* sp.[2] The chemical structure of **1** was elucidated mainly on the basis of spectroscopic studies. The absolute configurations of the five chiral centers of **1** have been determined by using NMR studies of the MTPA esters of **1** and its degradation products. Amphidinolide W exhibited potent cytotoxicity against murine lymphoma L1210 cells. Also, it is quite unique as it is the first and only macrolide in its family without an exomethylene unit.[3] Herein, we report the first total synthesis of amphidinolide W (**2**) and a revision of its C6 absolute stereochemistry (**1**).

As outlined in Figure 1, our synthetic strategy for amphidinolide W involves the assembly of C1−C9 segment **3** and C10−C20 segment **4** by cross metathesis of two terminal olefins, functional group transformation, followed by macrolactonization. Further disconnection of fragment **3** at the C3−C4 bond leads to keto-phosphonate **5** and aldehyde **6**. Subunit **4** was planned to be derived from lactone **7**, which would be synthesized using asymmetric dihydroxylation and alkylation as the key steps.

The synthesis of segment **3** is outlined in Scheme 1. The synthesis began with methylation of oxazolidinone derivative **8**[4] at −78 °C to provide **9** diastereoselectively (ratio 15:1). Basic hydrolysis of **9** and subsequent amidation afforded Weinreb amide **10**. Treatment of **10** with lithiated phosphonate gave *β*-ketophosphonate **5**. Horner−Emmons reaction between **5** and aldehyde **6**[5] furnished the corresponding *E*-enone exclusively without any epimerization.[6] Reduction of the resulting enone with Red-Al gave the corresponding ketone[7] which was protected as a dioxalane to afford **3**.

Synthesis of **4** is outlined in Scheme 2. Asymmetric dihydroxylation[8] of diene **11**[9] with AD-mix-α furnished the hydroxy-*γ*-lactone[10] which was protected as a TIPS-ether to furnish lactone **12**. Alkylation of **12** with LDA and MeI at −78 °C afforded **7** as the major diastereomer (11:1 dr).[11] Dibal-H reduction of **7** and subsequent Wittig reaction of the resulting hemiacetal provided *E*-olefin **13** exclusively. Alcohol **13** was converted to **4** by formation of the MOM-ether, deprotection of the TIPS-ether, followed by acetylation of the resulting alcohol.

Our assembly of the above subunits **3** and **4** by the key cross metathesis[12] is shown in Scheme 3. Among various protecting groups and catalysts surveyed, we found that the acetate protecting group and second generation Grubbs' catalyst[13] gave the optimum result, affording **14** along with its *Z*-isomer (*E*:*Z* ratio 11:1) in 85% yield. Dibal-H reduction of **14**, protection of the primary alcohol as the pivalate and the secondary alcohol as a TIPS ether, followed by reduction of pivalate with Dibal-H afforded **15** in 78% yield for four steps. Alcohol **15** was then converted to allylic bromide **16**. Formation of the phosphonium salt and subsequent Wittig reaction with propionaldehyde exclusively furnished *E*-olefin **17**. This was converted to acid **18** by deprotection of both TIPS groups,

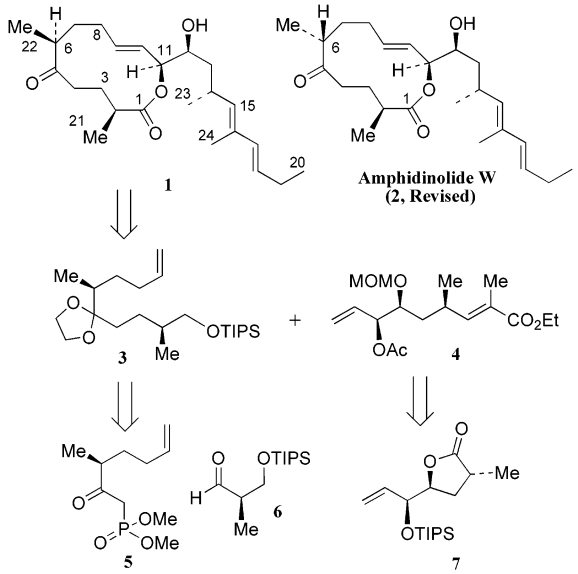
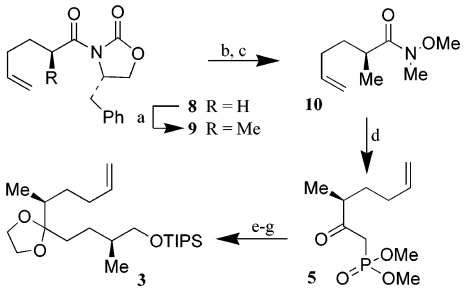


Figure 1. Retrosynthetic analysis of amphidinolide W.

Scheme 1 [a]



[a] Conditions: (a) NaHMDS, MeI, −78 °C, 87%; (b) LiOOH, aqueous THF, 0 °C; (c) MeONHMe·HCl, *N*-methylpiperidine, ^{i}BuOCOCl, −15 °C, 92% (two steps); (d) ^{n}BuLi, $MePO(OMe)_2$, −78 °C, 96%; (e) $Ba(OH)_2$, **6**, THF/H_2O, 85%; (f) Red-Al, CuBr, −20 °C, 90%; (g) *p*-TsOH, $HOCH_2CH_2OH$, $(EtO)_3CH$, 55 °C, 90%.

protection of the resulting diol as a diacetate, lipase PS-30-catalyzed selective removal of the primary acetate, followed by PDC oxidation of the resulting alcohol. Hydrolysis of acetate provided acid **19**. Macrolactonization of **19** under Yamaguchi conditions[14] afforded macrolactone **20** along with its C2-epimer **21** in 47% combined yield (3:1 mixture). Treatment of **20** with PPTS in aqueous acetone followed by $BF_3{\cdot}OEt_2$ removed the oxalane and MOM groups, furnish the presumed structure of amphidinolide W (**1**). Unfortunately, the ^{1}H and ^{13}C NMR spectra for **1** and for its C2-epimer **22** are not identical to those reported for natural amphidinolide W.[2]

Further comparison of the spectra of our synthetic proposed amphidinolide W (**1**) and the reported spectra of natural amphidinolide W revealed subtle discrepancies in the chemical shifts for the C6-chiral center. On the basis of these chemical shifts variations, we elected to synthesize the C6-epimer (*R*-configuration) of the

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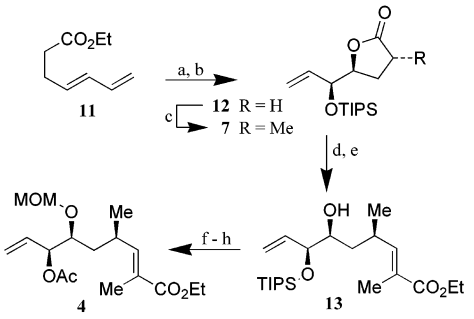
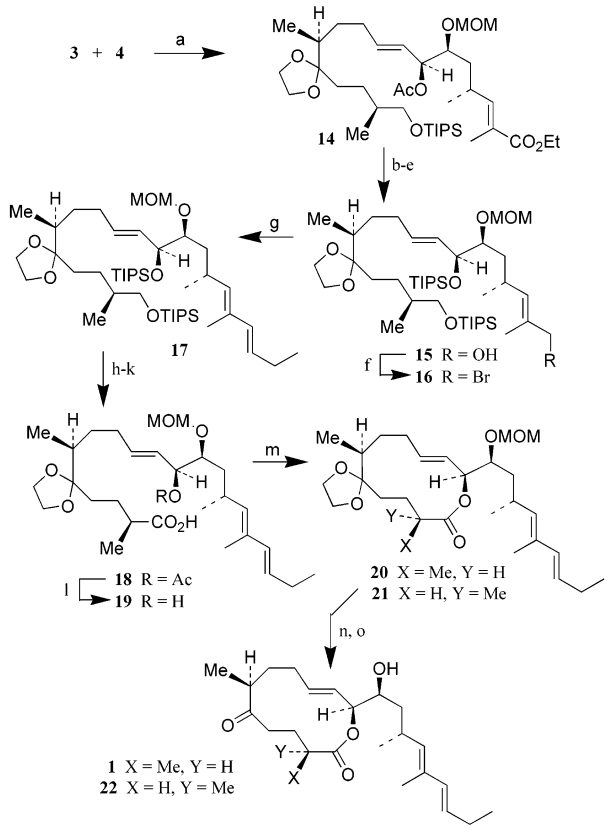
Scheme 2 [a]



[a] Conditions: (a) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, 43%; (b) TIPSOTf, 2,6-lutidine, 99%; (c) LDA, MeI, −78 °C, 82%; (d) Dibal-H, CH_2Cl_2, −78 °C; (e) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, 45 °C, 92% (two steps); (f) MOMCl, $^iPr_2NEt$, 94%; (g) TBAF, THF, 98%; (h) Ac_2O, Et_3N, DMAP, 94%.

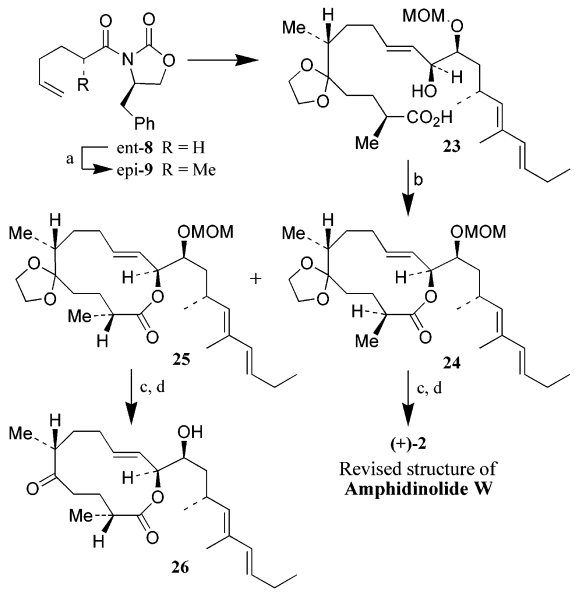
Scheme 3 [a]



[a] Conditions: (a) $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ (5 mol %), CH_2Cl_2, 45 °C, 85%; (b) Dibal-H, −78 °C, 88%; (c) PivCl, Py, 93%; (d) TIPSOTf, 2,6-lutidine, 99%; (e) Dibal-H, −78 °C, 96%; (f) CBr_4, PPh_3, 0 °C, 95%; (g) PBu_3, CH_3CN; then ^{t}BuOK, CH_3CH_2CHO, PhH/THF, 0 °C, 90%; (h) TBAF, THF, 99%; (i) Ac_2O, Et_3N, DMAP, 94%; (j) lipase PS-30, pH = 7.4, 95%; (k) PDC, DMF, 75%; (l) K_2CO_3, MeOH, 89%; (m) $^iPr_2NEt$, 2,4,6-$Cl_3C_6H_2COCl$, then DMAP, PhH 80 °C, 47%; (n) PPTS, acetone/H_2O, 40 °C, 87%; (o) $BF_3{\cdot}OEt_2$, Me_2S, −20 °C, 60%.

proposed structure **1**. As shown in Scheme 4, asymmetric alkylation of *ent*-**8** provided *epi*-**9** as a 12:1 mixture which was converted to C6-epimeric seco acid **23** following the synthetic steps described in Schemes 1 and 3. Macrolactonization[14] of **23** provided macrolactones **24** and **25** as a 1:1 mixture in 50% combined yield. Many attempts to improve the ratio for **24** have been so far unsuccessful. The stereochemical identities of the C2-methyl group of **24** and **25** were established by NOESY experiments. To our delight, removal of oxalane and MOM-protecting groups of **24** provided synthetic

Scheme 4 [a]



[a] Conditions: (a) NaHMDS, MeI, −78 °C, 87%; (b) $^iPr_2NEt$, 2,4,6-$Cl_3C_6H_2COCl$, then DMAP, PhH 80 °C, 50%; (c) PPTS, acetone/H_2O, 40 °C; (d) $BF_3{\cdot}OEt_2$, Me_2S, −20 °C, 50% (two steps).

amphidinolide W (**2**, $[\alpha]^{23}_D$ +8.1, *c* 1, $CHCl_3$),[15] whose spectral data (^1H and ^{13}C NMR) are identical to those of natural amphidinolide W.[2]

In summary, we have achieved the first total synthesis of amphidinolide W (**2**) and made a revision of the C-6 stereochemistry of structure **1** originally proposed for natural amphidinolide W.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for compounds **1**−**26** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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