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Highly stereoselective approach toward the synthesis of the macrolactone core of amphidinolide W

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ABSTRACT

The diastereoselective synthesis of the macrolactone core of amphidinolide W was successfully accomplished using Evans' asymmetric alkylation, Aldol reaction, Julia-Kocienski olefination, and Kita's macrocyclization protocol.

Amphidinolides constitute a group of structurally unique naturally occurring macrolides isolated from marine dinoflagellates of the genus amphidinium, which are symbionts of okinawan marine acoel flatworms *Amphiscolops* sp.[1] Owing to their profound biological activity (mainly antitumor properties) and scarce abundance, this family of macrolides set a great challenge to synthetic organic chemists.[2] Amphidinolide W is a 12-membered macrolide isolated by Kobayashi[3] in 2002 and showed potent cytotoxicity against murine lymphoma L1210 cells in vitro with an IC_{50} value of 3.9 μg/mL. It is structurally unique, being the first and only member in the family which lacks an *exo*-methylene unit.[3] Recently, a complete total synthesis of amphidinolide W was reported by Ghosh et al.[4] Their synthetic efforts were based on cross-metathesis to install the C9–C10 olefin and a Yamaguchi macrolactonization to make the lactone core. They also revised the originally proposed structure of Amphidinolide W (**1**) to (**2**), a stereochemical inversion at C6.[4] However, in the course of its total synthesis, problems such as epimerization were faced due to the intrinsic lability at the C2 center during base-catalyzed macrolactonization. Excited by the interesting structural features in combination with its fascinating biological activity, we wanted to develop a more potentially useful synthetic protocol toward its total synthesis (Fig. 1).

We initially focused our attention at devising a strategy toward the macrolactone core of revised amphidinolide W (**2**) that would provide exclusively *trans*-olefin and control the facile epimerization at C-2 and expecting that this method will also be applied to other related analogues.

Our initial target was the synthesis of the macrolactone core **3** containing four stereogenic centers and one $\Delta^{9,10}$ *E*-alkene which can be prepared from the sulfone **4**. The sulfone can be traced back to the fragment **6** which could in turn be obtained by a diastereoselective Evans aldol reaction followed by simple protecting group manipulations. At this point, we opt to take a simple aldehyde **5** for the synthesis of **3** which not only would help us to study the stereochemical course of reactions leading to the macrocycle but also would act as a surrogate to the side chain aldehyde required for the total synthesis of amphidinolide W (Scheme 1).

The synthesis commenced with the known oxazolidinone **9**,[5] which on stereoselective methylation provided **10** with high diastereoselectivity (17:1)[6] (^{1}H and ^{13}C NMR). The stereochemical outcome could be ascertained by hydrolyzing **10** to the corresponding acid and comparing the data with the reported values.[7]

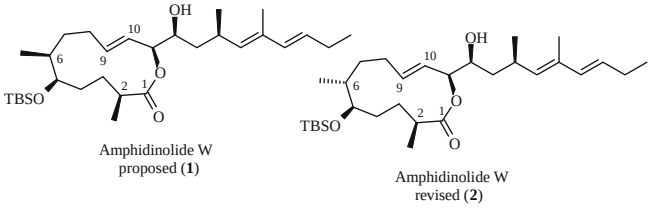

Figure 1. Proposed and revised structure of amphidinolide W.

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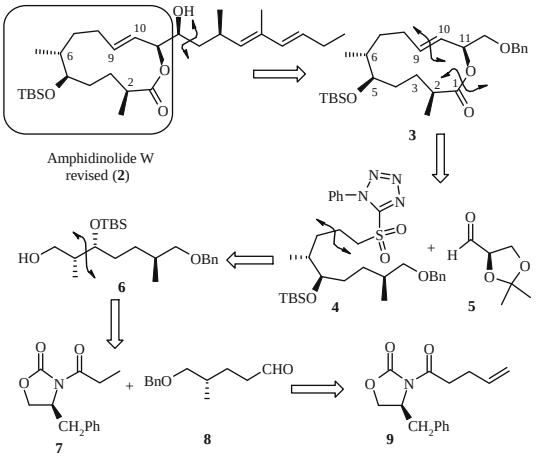
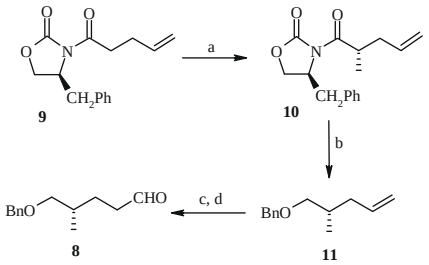


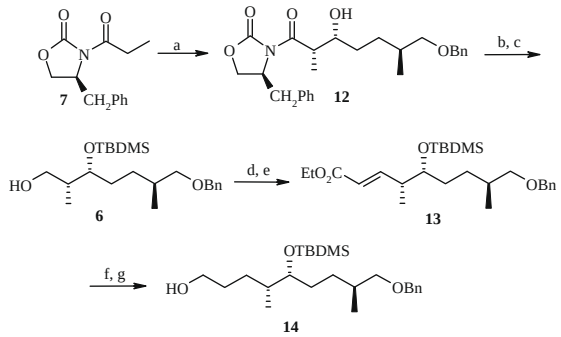
Scheme 1. Retrosynthetic analysis of amphidinolide W.



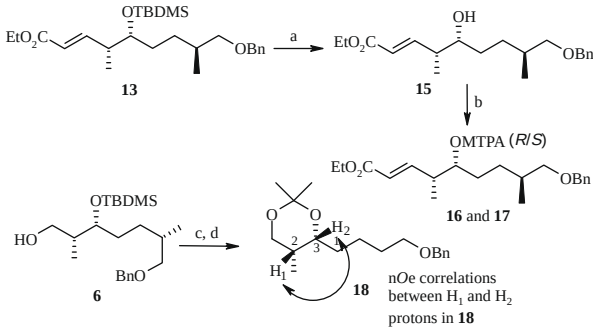
Scheme 2. Reagents and conditions: (a) MeI, NaHMDS, −78 °C, 4 h, 85%; (b) (i) LAH, Ether, 0 °C, 2 h, (ii) NaH, BnBr, THF, 0 °C–rt, 7 h, 86% over two steps; (c) $BH_3{\cdot}SMe_2$, THF, 0 °C, 5 h, NaOH (10%), H_2O_2 (30%), 16 h, 88%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 4 h, 94%.

Reductive removal of auxiliary,[8] followed by sequential benzylation, hydroboration, and Dess Martin oxidation[9] afforded the aldehyde **8** (Scheme 2) which was used for the next Evans' aldol reaction.

Having aldehyde **8** in hand, the Evans *syn* aldol reaction with oxazolidinone **7**[5a] using Bu_2BOTf at −78 °C afforded the desired Evans' *syn*-isomer **12** with good yield and high diastereoselectivity (19:1).[10] The relative stereochemistry of the newly generated stereocenters was initially predicted through literature precedence[10] and further confirmation of the absolute configuration was achieved in the latter part of the synthesis. Protection of the secondary hydroxyl as a TBS ether and removal of the oxazolidinone using $LiBH_4$[11] provided the alcohol **6**. Oxidation of the primary alcohol with PDC and a two-carbon Wittig homologation furnished the α,β-unsaturated ester **13** (*E*:*Z* = 9:1). Chemoselective reduction of the double bond using $NiCl_2/NaBH_4$[12] and subsequent $LiAlH_4$ reduction of ester furnished the alcohol **14** in 89% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) Bu_2BOTf, DIPEA, CH_2Cl_2, 0 °C; **8**·CH_2Cl_2, −78 °C, 7 h, 75%; (b) TBDSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C–rt, 0.5 h, 95%; (c) $LiBH_4$, EtOH/THF, 0 °C–rt, 6 h, 83%; (d) PDC, CH_2Cl_2, rt, 2 h, 81%; (e) $Ph_3P{=}CHCO_2Et$, benzene, rt, 10 h, 79%; (f) $NiCl_2$, $NaBH_4$, MeOH, 0 °C, 0.5 h, 98%; (g) LAH, THF, 0 °C, 2 h, 89%.



Scheme 4. Reagents and conditions: (a) HF–Py, Py, THF, 0 °C–rt, 6 h, 73%; (b) *R*/*S*-MTPA acid, DCC, DMAP, CH_2Cl_2, rt, 8 h, 73% for *R*-isomer and 76% for *S*-isomer; (c) TBAF, THF, rt, 1 h, 90%; (d) 2,2-dimethoxy propane, acetone, *p*-TSA, rt, 4 h, 74%.

Before the Julia–Kocienski reaction, the absolute configurations of the newly generated stereocenters of **6** were investigated. Removal of silyl ether of **13** with HF–Py in Py/THF at room temperature[13] produced the secondary alcohol **15** which was converted into the respective MTPA esters[14] *R* (**16**) and *S* (**17**) to evidence our initially proposed stereochemistry of hydroxyl group as '*R*' configuration. Further establishment of the stereochemistry of the adjacent methyl group was confirmed by converting **6** into its isopropylidene derivative **18** where NOESY correlations witnessed the *syn* alignment of the two adjacent chiral centers (Scheme 4). For instance the protons H_1 and H_2 showed significant NOE enhancements in **18**, hence establishing the stereochemistry of the methyl center to be '*R*' configuration.

The most crucial step was to perform the Julia–Kocienski reaction to obtain the $\Delta^{9,10}$ *E*-alkene, exclusively. For that, Mitsunobu substitution[15] of the primary alcohol of **14** by 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation[16] provided sulfone **4** in good yield.[17] For the Julia–Kocienski[18,19] olefination, a variety of conditions was exhaustively investigated. The best results were obtained under conditions using KHMDS in DME at −60 °C with aldehyde **5**, prepared from D-mannitol,[20] producing the desired olefin **19** in 82% yield with exclusive *E*-selectivity.[21] Confirmation of *E*-selectivity was achieved from ^1H NMR spectrum in which the two olefinic protons at δ 5.43 and 5.76 ppm displayed a vicinal coupling constant of J = 15.3 Hz. The next step was the crucial macrolactonization. For this purpose, the isopropylidine group was selectively cleaved under mild Lewis acid conditions.[22] Subsequent Birch reduction with Li, liq. NH_3 at −78 °C furnished triol **20** in overall good yield. Bu_2SnO-mediated selective protection of homoallylic primary hydroxyl as its benzyl ether **21** followed by oxidation of the remaining primary hydroxyl to the seco acid was achieved via a two step protocol. Oxidation with BAIB in the presence of TEMPO[23] and subsequent oxidation of the intermediate aldehyde with $NaClO_2$[24] in presence of NaH_2PO_4 as buffer furnished **22**. The seco acid **22** was initially tested for Yamaguchi lactonization[25] but unfortunately it furnished an inseparable mixture of products **3** and **23** (1:1) in 55% combined yield, which was confirmed from its ^1H and ^{13}C NMR. Interestingly, when lactonization was performed following Kita's conditions,[26,27] single desired isomer of the macrolactone derivative **3** was obtained in 42% yield. Rest of the mass was accountable for an intractable mixture of products and 35% starting material which was recovered from the reaction mixture. The compound was characterized by its

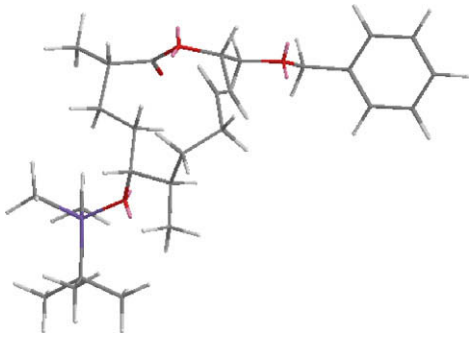


Figure 2. Minimum energy diagram of **3**.

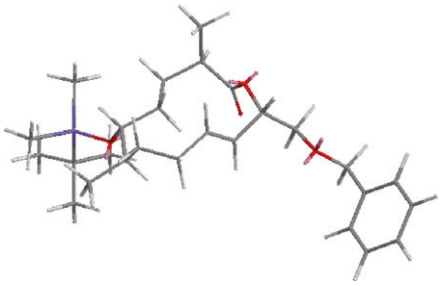


Figure 3. Minimum energy diagram of **23**.

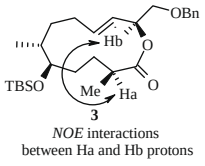
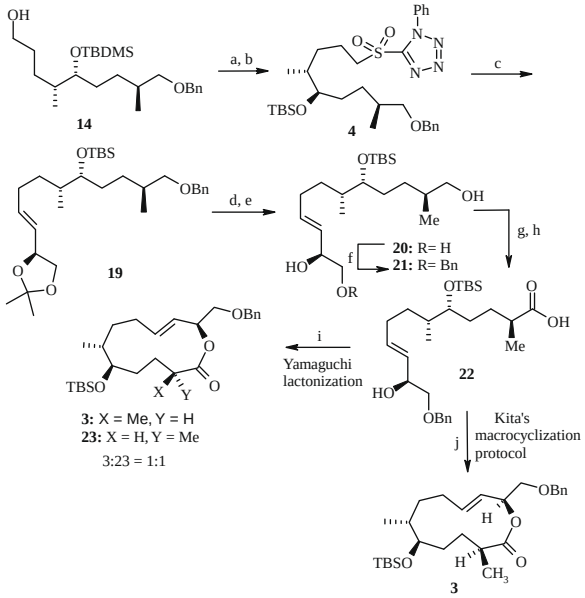


Figure 4.



Scheme 5. Reagents and conditions: (a) PTSH, DIAD, Ph_3P, THF, 0 °C, 89%; (b) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 0 °C–rt, 92%; (c) KHMDS, DME, **5**, −60 °C, 2 h, 82%; (d) $Zn(NO_3)_2{\cdot}6H_2O$, CH_3CN, 50 °C, 74%; (e) Li, liq. NH_3, −78 °C, 78%; (f) Bu_2SnO, BnBr, TBAI, toluene, reflux, 84%; (g) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, rt, 92%; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (3:1), 87%; (i) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, rt; DMAP, benzene, 80 °C, 55% combined yield; (j) EtOCCH, [{Ru(*p*-cymene)Cl_2}$_2$], toluene, 0 °C–rt, 30 min; CSA, toluene, rt–50 °C, 2 h, 42%.

mass, elemental analysis, and NMR studies.[28] As per the minimum energy diagram of **3** (Fig. 2) and **23** (Fig. 3), there should be a significant NOE effect between H_a and H_b protons in **3**. The stereochemical identifications for the desired isomer were established by NOESY experiment as shown in Figure 4, which showed considerable NOE enhancement between H_a and H_b protons. This information not only resolved the possible drawback faced in the Yamaguchi's lactonization (Scheme 5) but also can be utilized to synthesize other related bioactive macrolactone compounds with high selectivity.

In conclusion, we have developed a highly efficient route to the macrolactone core of amphidinolide W. The synthesis features highly stereo and regioselective incorporation of chiral centers utilizing Evans' asymmetric alkylation and aldol reactions together with the execution of a highly stereoselective Julia–Kocienski olefination for the construction of the $\Delta^{9,10}$ *E*-alkene. Selective oxidation processes using BAIB in presence of TEMPO are well suited in the synthesis. Of particular note is the final lactonization using Kita's protocol which selectively produced only the required isomer thus overcoming the difficulty of epimerization encountered in the Yamaguchi lactonization. Further insight into the total synthesis of this natural product is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.088.

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127.5, 128.3, 129.7, 131.3, 133.1, 138.7, 153.5; ESI-MS *m*/*z* 623.3904 $(M+Na)^+$. Anal. Calcd for $C_{31}H_{48}N_4O_4SSi$: C, 61.96; H, 8.05; N, 9.32. Found: C, 61.82; H, 7.97; N, 9.16.

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21. $[\alpha]_D^{25}$ +17.9 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$): 2929, 1591, 1455, 1379,1252, 1061, 836, 773, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.01 (s, 3H), 0.79 (d, 3H, *J* = 6.7 Hz), 0.86 (s, 9H), 0.92 (d, 3H, *J* = 6.8 Hz), 1.00 (m, 1H), 1.16 (m, 1H), 1.37 (s, 3H), 1.41 (s, 3H), 1.43–1.52 (m, 4H), 1.71 (m, 1H), 1.93–2.01 (m, 2H), 2.08 (m, 1H), 3.23 (dd, 1H, *J* = 6.6, 9.0 Hz), 3.30 (dd, 1H, *J* = 6.2, 9.0 Hz), 3.48 (m, 1H), 3.53 (t, 1H, *J* = 8.0 Hz), 4.04 (dd, 1H, *J* = 6.1, 8.0 Hz), 4.45 (m, 1H), 4.49 (s, 2H), 5.41 (dd, 1H, *J* = 8.0, 15.3 Hz), 5.76 (dt, 1H, *J* = 6.8, 15.3 Hz), 7.32-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5, −4.2, 14.1, 17.2, 18.1, 25.9, 26.7, 29.9, 30.3, 30.7, 31.8, 33.7, 37.1, 69.5, 72.97, 75.8, 75.9, 77.4, 108.97, 127.0, 127.4, 127.5, 128.3, 136.3, 138.8; ESI-MS *m*/*z* 527.4708 $(M+Na)^+$. Anal. Calcd for $C_{30}H_{52}O_4Si$: C, 71.38; H, 10.38. Found: C, 71.14; H, 10.22.
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28. $[\alpha]_D^{25}$ +29.0 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 2929, 1722, 1598, 1384, 1255, 1115, 1026, 772, 618; ^1H NMR (500 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.85 (d, 3H, *J* = 6.7 Hz), 0.87 (s, 9H), 1.18 (d, 3H, *J* = 6.9 Hz), 1.36–1.42 (m, 2H), 1.49–1.57 (m, 5H), 1.75 (m, 1H), 2.14 (m, 1H), 2.26 (m, 1H), 3.28 (m, 1H), 3.57 (dd, 1H, *J* = 4.4, 10.8 Hz), 3.61 (dd, 1H, *J* = 6.7, 10.8 Hz), 4.58 (ABq, 2H, *J* = 12.4 Hz), 5.44–5.53 (m, 2H), 5.91 (ddd, 1H, *J* = 6.2, 9.4, 15.5 Hz), 7.28–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.9, −4.4, 17.5, 17.8, 18.2, 25.95, 28.4, 30.2, 30.4, 33.3, 34.1, 41.7, 70.7, 72.4, 73.2, 74.0, 127.5, 127.56, 127.6, 128.4, 138.2, 138.3, 175.4; ESI-MS *m*/*z* 483.243 $(M+Na)^+$. Anal. Calcd for $C_{27}H_{44}O_4Si$: C, 70.39; H, 9.63. Found: C, 70.34; H, 9.55.