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COMMUNICATION

Ring-closing metathesis (RCM) based synthesis of the macrolactone core of amphidinolactone A†

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A convergent synthesis of the macrolactone core of amphidinolactone A has been achieved, in a 10 step linear sequence with 32% overall yield, through a ring-closing metathesis reaction as the macrolactonization step. The RCM precursor was obtained by the union of acid and alcohol fragments derived from (*R*)-epichlorohydrin and (*R*)-2,3-*O*-isopropylidene glyceraldehyde, respectively.

In 2007, Kobayashi *et al.* isolated amphidinolactone A (**1**), a cytotoxic 13-membered macrolide, from symbiotic dinoflagellate *Amphidinium* sp. (Y-25) separated from an Okinawa a marine acoel flatworm *Amphiscolops* sp.[1] The relative and absolute stereochemistry of amphidinolactone A (**1**) have been elucidated on the basis of extensive spectral analysis followed by total synthesis.[2] The interesting biological profile as well as the structural complexity of amphidinolactone A (**1**) (Fig. 1) has attracted the attention of synthetic organic chemists worldwide. Recently, we reported a concise and efficient total synthesis[3] of amphidinolactone A *via* stereoselective intramolecular Nozaki–Hiyama–Kishi reaction.

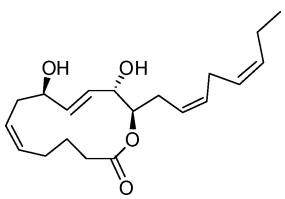
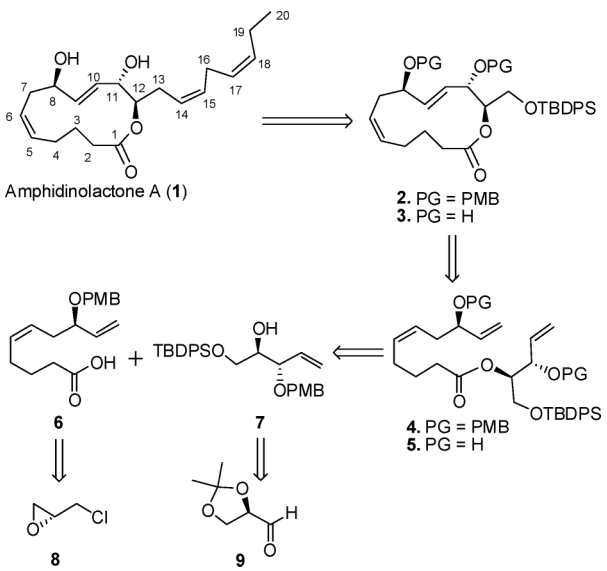


Fig. 1 Structure of amphidinolactone A (**1**).

Construction of lactone through the formation of C–C bond and particularly by intramolecular ring-closing metathesis[4] reaction stands as a promising tool for the synthesis of macrolides and heterocycles. The influence of protecting groups and the substrate-specific nature of the ring-closing metathesis reaction have been reported previously.[5] During our studies on the total synthesis of nonenolide and decarestrictine C1 and C2, we observed a complete control of the double bond geometry by the protecting groups during the ring-closing metathesis reaction.[5b,e] In continuation of our interest in exploring the substrate directed ring-closing metathesis reaction for macrolide synthesis, we planned to synthesize initially the macrolactone core of amphidinolactone A.

According to our retrosynthetic analysis of amphidinolactone A (**1**) shown in Scheme 1, **3** could be achieved through ring-closing metathesis reaction of **5** which in turn could be obtained by esterification of acid **6** with alcohol **7**. Acid fragment **6** and alcohol fragment **7** could be obtained from (*R*)-epichlorohydrin (**8**) and (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**9**), respectively.



Scheme 1 Retrosynthetic analysis of amphidinolactone A (**1**).

Chiral epoxide **8** obtained through Jacobsen's hydrolytic kinetic resolution protocol,[6] was taken as the starting material for the synthesis of acid fragment **6**. The epoxide **8** was treated with lithium acetylide prepared from TBS-protected alkyne **10** using *n*-BuLi in THF at −78 °C to afford **11** in 92% yield.[7] The epoxidation of the resulting chlorohydrin **11** proceeded smoothly with NaH in THF at 0 °C to obtain **12** in 91% yield. Partial hydrogenation was achieved with Lindlar catalyst[8] to furnish the *Z*-olefin derivative **13** in 96% yield. One-carbon homologation[9] with dimethyl sulfonium methylide at −10 °C afforded the allylic alcohol **14** in 85% yield. Protection of the secondary hydroxyl group as its PMB

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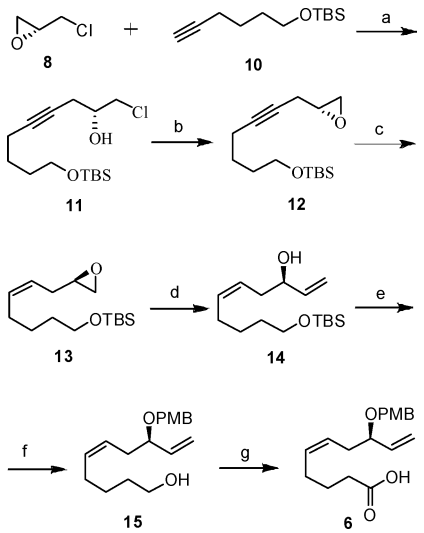
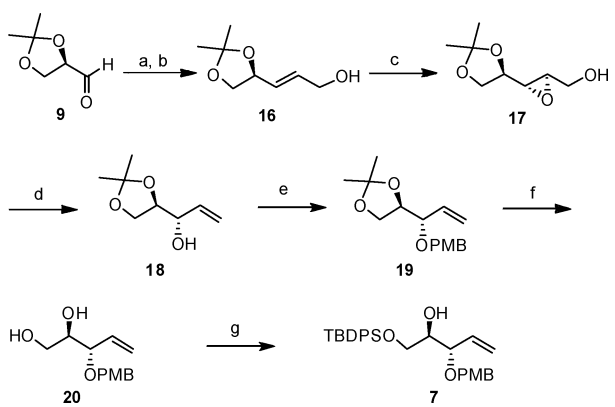
ether followed by desilylation with *p*-TsOH in MeOH at room temperature gave the primary alcohol **15** in 81% yield over two steps. Treatment of the resulting primary hydroxyl group with TEMPO[10] and BAIB furnished the corresponding aldehyde which on further oxidation under Pinnick[11] conditions furnished the acid fragment **6** in 89% yield over two steps (Scheme 2).



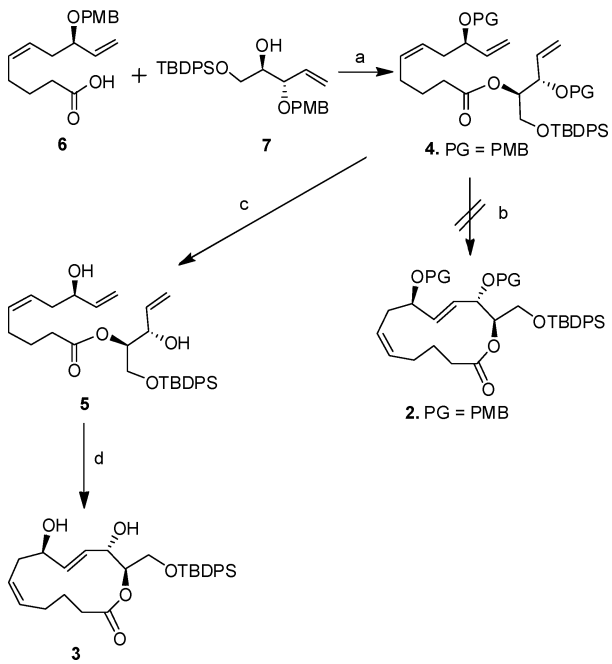
Scheme 2 *Reagents and conditions*: (a) *n*-BuLi, $BF_3{\cdot}(OEt)_2$, **10**, –78 °C, 1 h, 92%; (b) NaH, THF, 0 °C, 1 h, 91%; (c) H_2, Pd/C on $CaCO_3$, quinoline, rt, 2 h, 96%; (d) Me_3SI, *n*-BuLi, THF, –10 °C, 2 h, 85% (e) PMB-Br, NaH, THF, 4 h, 91% (f) *p*-TsOH, MeOH, 0 °C–rt, 1 h, 89%; (g) (i) TEMPO, BAIB, CH_2Cl_2, 30 min, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 2 h, 89% (over two steps).

Synthesis of fragment **7** was commenced with two-carbon homologation of the known aldehyde (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**9**)[12] to give α,β-unsaturated ester in 85% yield which was converted to the corresponding *E*-allylic alcohol **16** under standard reaction conditions (Scheme 3). Sharpless asymmetric epoxidation[13] of **16** with (–)-DET and TBHP afforded 2,3-epoxy alcohol **17** in 93% yield (94 : 6 ratio with the required isomer as the major product). The primary hydroxyl group of **17** was converted to the corresponding iodide with I_2, TPP and imidazole in THF and subsequent reductive elimination[14] of iodine with activated Zn dust in EtOH provided the allylic alcohol **18** in 85% yield over two steps. The resulting secondary hydroxyl group was protected as its PMB ether to obtain **19** in 92% yield. Deprotection of the isopropylidene group with *p*-TsOH in MeOH[15] at room temperature afforded diol **20** in 87% yield. The primary hydroxyl group of diol **20** was selectively protected as its TBDPS-ether by using TBDPS-Cl and imidazole in THF to obtain the alcohol fragment **7** in 89% yield.



Scheme 3 *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 2 h, 85%; (b) DIBAL-H, CH_2Cl_2, 0 °C, 30 min, 84%; (c) (–)-DET, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, –20 °C, 12 h, 93%; (d) (i) I_2, PPh_3, imidazole, THF, 0 °C, 10 min; (ii) activated Zn, NaI, EtOH, reflux, 85% (for 2 steps); (e) PMB-Br, NaH, THF, 5 h, 92%; (f) CSA, MeOH, 0 °C, 2 h, 87%; (g) TBDPS-Cl, imidazole, THF, 3 h, 89%.

Our next target was to couple both the fragments and investigate the critical ring-closing metathesis reaction. As per our earlier reports, we followed the Yamaguchi conditions[16] for the esterification reaction. In this case, the yield was only 30–35%. However, a better result was achieved by uniting both the coupling partners with EDCI and DMAP in CH_2Cl_2 to afford the triene ester **4** in 90% yield (Scheme 4).[17] This sets the stage for the crucial RCM reaction. When ester **4** was refluxed with Grubbs' II generation catalyst in CH_2Cl_2 under high dilution conditions (0.001 M), the reaction did not proceed at all. The extent of bias if any conferred by the protecting groups on the outcome of the ring-closing metathesis reaction could not be predicted with certainty. We envisaged that PMB-protecting groups around the reacting centers might act as a temporary constraint to stop them from coming close enough for the reaction to happen. This prediction was also supported by computational analysis (Fig. 2) where the di-PMB protected product **2** showed a minimum energy of 44.18 kcal mol^{-1} and its protection free counterpart **3** showed 24.71 kcal mol^{-1} as well as experimental studies. To further prove our predictions, di-PMB protected ester **4** was treated with DDQ[18]



Scheme 4 *Reagents and conditions*: (a) EDCI, DMAP (cat), CH_2Cl_2, 0 °C, 5 h, 90%; (b) Grubbs' II generation catalyst, CH_2Cl_2, reflux, no reaction; (c) DDQ, $CH_2Cl_2 : H_2O$ (9 : 1), 0 °C, 93%; (d) Grubbs' II generation catalyst, CH_2Cl_2, reflux, 76%.

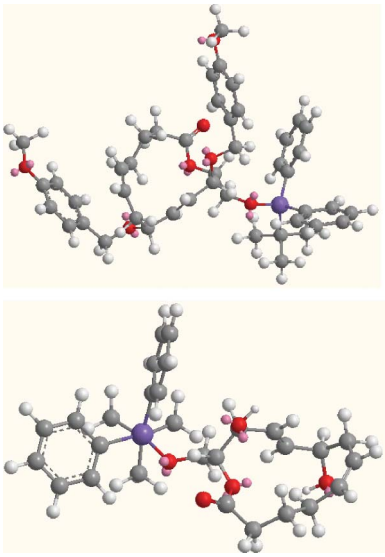


Fig. 2 Minimum energy calculated for di-PMB protected lactone core **2** (44.18 kcal mol^{-1}) and diol-lactone **3** (24.71 kcal mol^{-1}) of amphidinolactone A.

in $CH_2Cl_2 : H_2O$ (9 : 1) to obtain diol **5** in 93% yield (Scheme 4). Treatment of diol **5** with Grubbs' II generation catalyst[19] in refluxing CH_2Cl_2 under high dilution (0.001 M) conditions smoothly furnished the required 13-membered lactone ring system **3** present in amphidinolactone A (**1**) in 76% yield.

The geometry (*trans*) of the newly formed double bond was established by its coupling constant, while one of the olefinic proton signals appeared at δ 5.66 ppm as a doublet of a doublets (J_{trans} coupling constant 15.7 Hz) and other olefinic proton signals appeared at their respective chemical shifts. The spectral and analytical data were in good agreement with the constitution and configuration of the assigned structure for **3**.

In summary, the steric effect of protecting groups on the ring-closing metathesis reaction for the construction of 13-membered lactone ring system of amphidinolactone A has been demonstrated. The coupling partners have been synthesized from commercially available starting materials in a concise manner. Study of steric bulk in conjunction with the absolute configuration at the two hydroxyl centers towards RCM reaction for the construction of 13-membered lactone ring as well as the total synthesis of amphidinolactone A, following ring-closing metathesis reaction as the crucial macrolactonization step is under progress and will be reported in due course.

Acknowledgements

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