Synthetic Studies toward the Total Synthesis of Amphidinolide H1

Lisheng Deng, Zhixiong Ma, Gang Zhao*

Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. of China
Fax +86(21)64166128; E-mail: zhaog@mail.sioc.ac.cn

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Abstract: A convergent synthesis of the macrolide core as the immediate precursor to amphidinolide H1 is described, which features a palladium-catalyzed Stille cross-coupling, a methyl ketone diastereoselective aldol reaction, a Mitsunobu esterification, and an intramolecular ring-closing metathesis (RCM) reaction to construct the 26-membered macrocycle as key steps.

Key words: amphidinolide H1, macrolide, aldol reaction, RCM reaction, Mitsunobu reaction

Amphidinolides are a family of structurally diverse macrolides that have been isolated from marine dinoflagellates of the genus Amphidinium living in symbiosis with Okinawan acoel flatworm Amphiscolops sp.[1,2] There are some common structural features for the amphidinolides, for example, they have one or more *exo*-methylene units, a highly oxygenated and stereochemically rich macrocycle ranging in size from 12 to 29 atoms. Due to their good biological activity, structural complexity, and natural scarcity, amphidinolides have been very attractive target molecules for organic chemists.[3,4]

Amphidinolide H1 (**1**) and its congeners H2–H5 are a group of 26-membered macrolides, which possess some unique structural features such as an allyl epoxide or vicinally located one-carbon branches.[5] More importantly, **1** exhibits extremely potent cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines (IC_{50} values: 0.48 ng/mL and 0.52 ng/mL, respectively).[6] So far, considerable efforts have been directed toward the syntheses of **1** and structurally related amphidinolide B and G.[7,8] Very recently, the Fürstner group reported the first total syntheses of amphidinolide H and G.[4b] On the other hand, we have finished the total synthesis of amphidinolide T3 and formal synthesis of amphidinolide T4,[4a] and the sythesis of segment C14–C26 of amphidinolide H1.[7g] As a part of our ongoing project to synthesize some members of the amphidinolide family, herein, we would like to describe our studies on the total synthesis of Amphidinolide H1 (**1**), and our successfully stereoselective synthesis of its precursor **2**.

According to the synthetic strategy we reported recently (Scheme 1),[7g] we envisioned that amphidinolide H1 (**1**) could be achieved by deprotecting the MOM group of its precursor, macrocycle **2**, while **2** could be formed by an intramolecular RCM from alkene **3**, which should be available through an aldol addition between the aldehyde **4** and methyl ketone **5**. Finally, a Stille coupling of compounds **6** and **7** would lead to the fragment **4**, and the latter fragment **5** could be assembled from the subunits **8** and **9** via a Mitsunobu esterification.

The synthesis of vinyl iodide **6** could be achieved from the known chiral alcohol **10**,[7g] which can be easily prepared in four steps either from commercially available methyl (*R*)-3-hydroxyl-2-methylpropionate or by the Lewis acid mediated alkylation of *N*-propionyl-oxazolidinone with BOMCl (Scheme 2).[4a,9] After it was protected as a TBS ether, the benzyl group of **11** was removed in the presence of lithium and ammonia at –78 °C to provide **12** in 99% yield. Oxidation of **12** using the Dess–Martin periodinane followed by treatment of the corresponding aldehyde with CBr_4 and Ph_3P led to the α,α-dibromoalkene **13** in 88% yield,[10] which was then converted into alkyne **14** (95%) by using *n*-butyllithium. Treatment of **14** with trimethylaluminum and bis(cyclopentadienyl)zirconium(IV) dichloride in CH_2Cl_2,[11] followed by iodination of the intermediate in situ afforded *E*-vinyl iodide fragment **6** in 91% yield.

As shown in Scheme 3, the synthesis of vinyl stannane fragment **7** was started from alcohol **16**, which was conveniently prepared via two steps by a known procedure.[8s,12] Alcohol **16** was treated with mesyl chloride and triethylamine in CH_2Cl_2 at 0 °C, and the resulting mesylate was then converted into cyanide **17** in 78% yield through a S_N2 reaction with sodium cyanide. Diisobutylaluminum hydride (DIBAL-H) reduction of cyanide **17** and subsequent Wittig reaction using $Ph_3P{=}CHCO_2Et$ provided a *E*-olefin **18** in 70% yield in two steps. After reduction of the unsaturated ester **18** with DIBAL-H, the resulting alcohol was protected with TBSCl to give silyl ether **19**. Subsequent halogen–lithium exchange in the presence of *tert*-butyllithium followed by quenching with *n*-Bu_3SnCl proceeded smoothly to afford the corresponding vinyl stannane **20** in 76% yield. Finally, desilylation of **20** with TBAF followed by a Sharpless epoxidation[13] of the allylic alcohol **21** gave **7** (86%) as a single isomer.

With the two required components of **6** and **7** in hand, we examined several reaction conditions for the Stille cross-coupling between the vinyl iodide **6** and vinyl stannane **7**.[14] Using catalytic $PdCl_2$(dppf) in the presence of freshly prepared CuCl in MeCN at 60 °C (Scheme 4), a satisfying result could be obtained with the desired conjugated diene **22** in 80% yield. Then diene **22** was subjected to Parikh–

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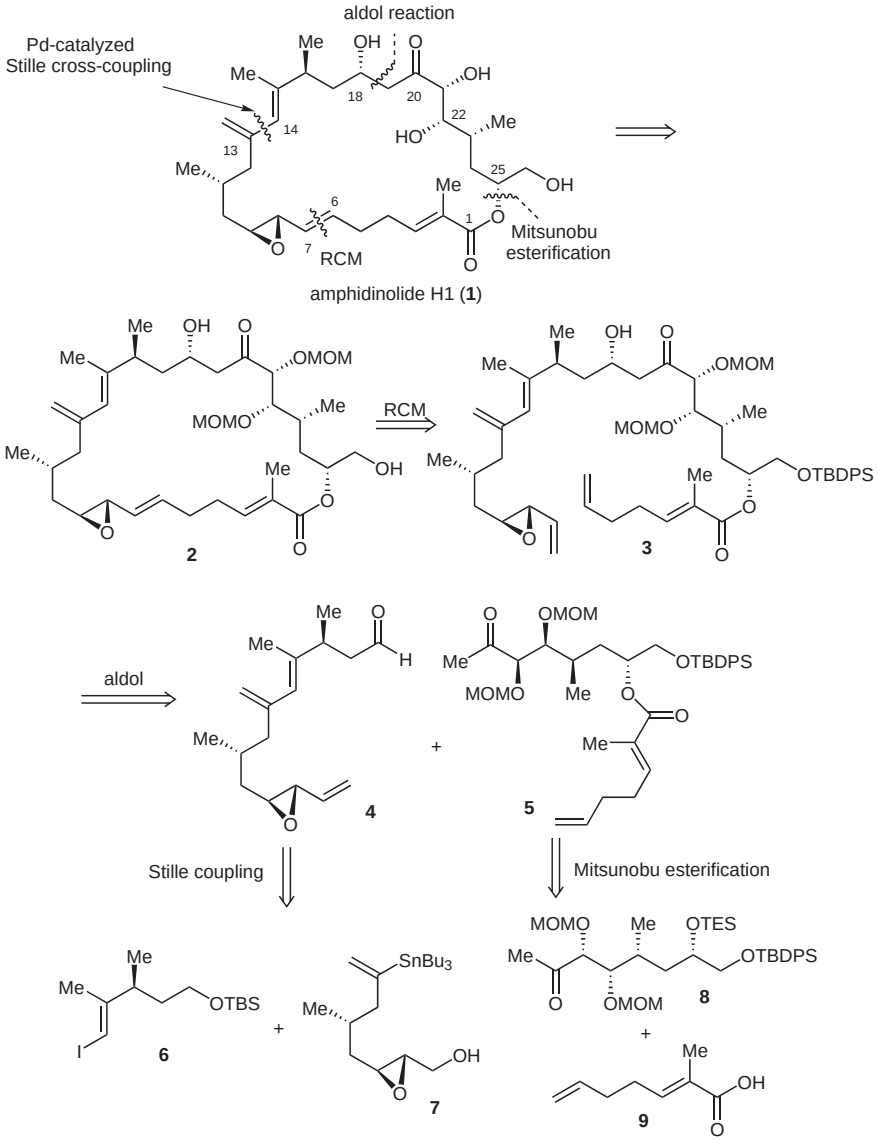
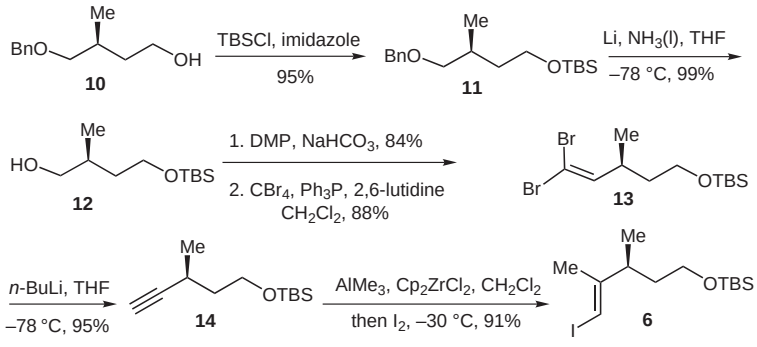


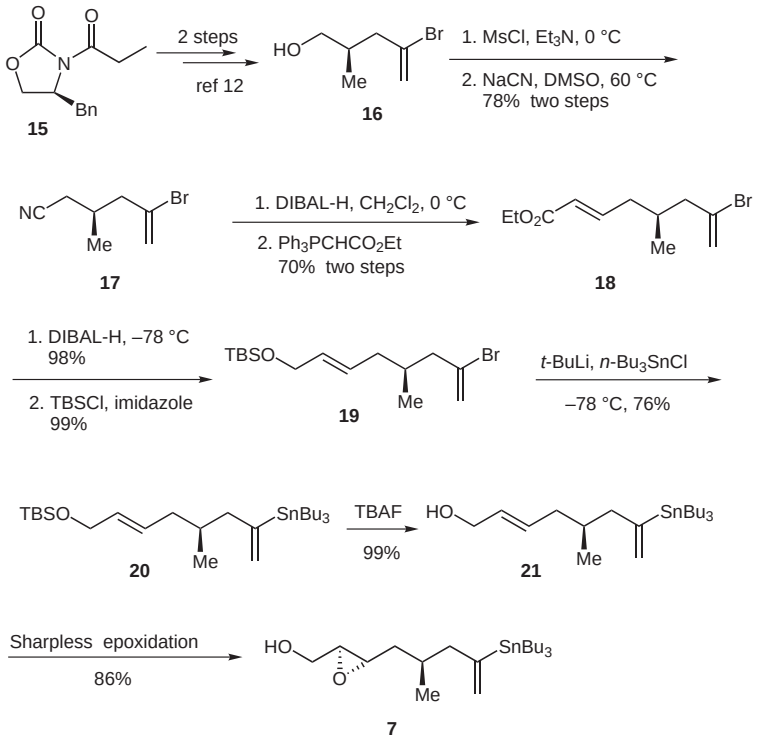
Scheme 1 Retrosynthetic analysis of amphidinolide H1 (**1**)



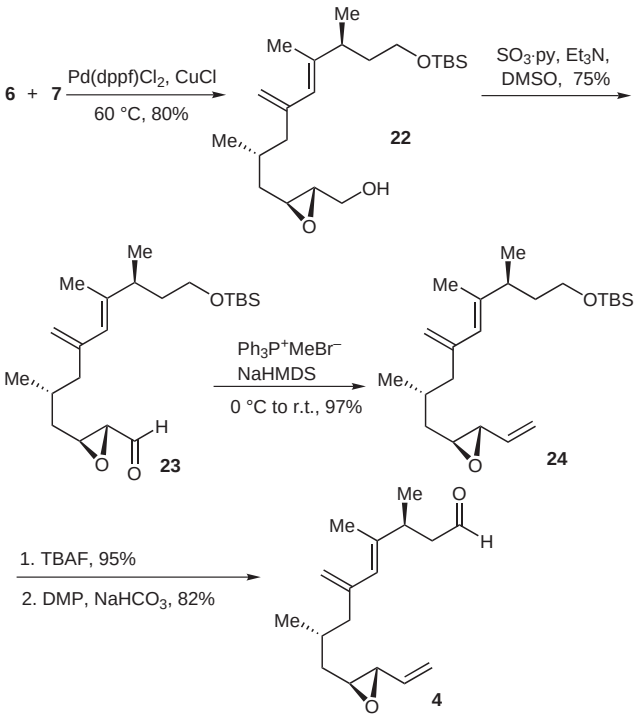
Scheme 2 Preparation of segment **6**

Doering oxidation[15] to give aldehyde **23** (75%). Wittig methylenation of **23** with $Ph_3P^+CH_3Br^-$ effectively furnished olefin **24** in 97% yield. Removal of TBS group in **24** with TBAF followed by oxidation of the resulting alcohol using DMP as an oxidant successfully led to the aldehyde **4**.[16] It is noteworthy that the overall yield was up to 16% in fourteen steps from compound **16** to **4**.

The known ketone **8**,[7g] which can be prepared in a large scale from the commercially inexpensve L-glutamic acid, was chosen as the starting material to synthesize methyl ketone **5**. After deprotection of the TES ether of **8** fol-



Scheme 3 Preparation of segment **7**

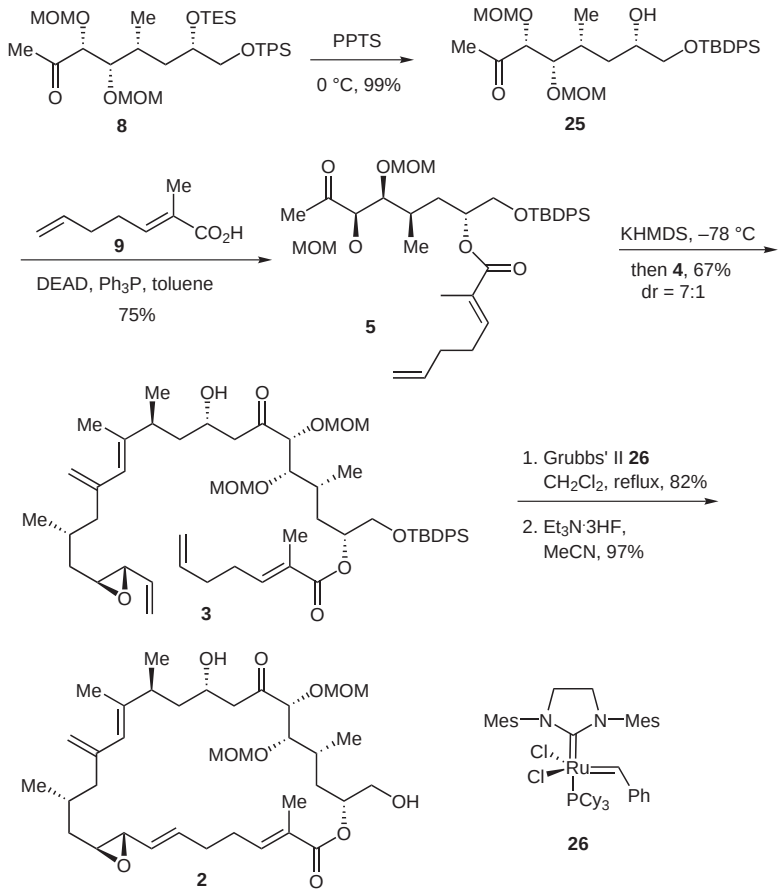


Scheme 4 Preparation of aldehyde **4**

lowed by a Mitsunobu esterification[17] with acid **9**,[18] the ketone **5** was obtained in 74% yield over two steps. The next key step was an aldol coupling between aldehyde **4** and ketone **5**. In contrast to earlier work on synthesis of segment C14–C26,[7g] satisfying yield and selectivity were not observed by using enolate derived from LHMDS in THF. However, to our delight, good selectivity (dr = 7:1) in favor of the Felkin product was obtained when KHMDS was used as the base and the stereochemistry of newly formed C18 was established by Mosher ester method.[19]

With compound **3** in hand, the accomplishment of the total synthesis of amphidinolide H1 (**1**) was around the corner. The next crucial step would be the ring-closing metathesis to construct the macrocycle. As we expected, the RCM reaction mediated by Grubbs second-generation ruthenium catalyst **26** gave the desired macrocycle with the 6*E*-stereoisomer as a single product in 82% yield,[20] which was easily converted into diol **2**[21] in the presence of $Et_3N{\cdot}3HF$ and Et_3N in excellent yield (97%).[22] The final work was to remove the two MOM groups of the diol **2** to liberate the amphidinolide H1 (**1**). However, experiments proved that it was quite problematic, due to existence of allyl epoxide. Many attempts failed. Finally, target compound **1** was observed by LCMS when **2** was treated with boron trifluoride etherate and methyl sulfide under –20 °C, accompanied by considerable impurities, thus it was difficult to get pure product of amphidinolide H1 (**1**).[23]

In summary, we have studied the total synthesis of amphidinolide H1 via a highly flexible, concise, and convergent strategy using the readily available and inexpensive chiral pool. Although the final step to accomplish the total synthesis was failed so far, the intermediate precursor **2** to the macrolide **1** was synthesized successfully in 19 steps for the longest linear sequence and with 6.1% overall yield. The key setps include a palladium-catalyzed Stille cross-coupling, a methyl ketone diastereoselective aldol reaction, a Mitsunobu esterification, and an intramolecular RCM to construct the 26-membered macrocycle, which is



Scheme 5 Completion of the synthesis of **1**

also amendable to its analogues amphidinolides B and H. Continued studies toward these total syntheses are currently under way in our laboratory.

Acknowledgment

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(16) Aldehyde **4**: $[\alpha]_D^{24}$ –4.0 (*c* 0.60, $CHCl_3$). IR (film): 2958, 2925, 1726, 1459, 1378, 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.60–5.40 (m, 3 H), 5.27–5.24 (m, 1 H), 4.96 (s, 1 H), 4.81 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 2 H), 3.05 (dd, *J* = 1.8, 6.9 Hz, 1 H), 2.84–2.80 (m, 1 H), 2.32–2.25 (m, 1 H), 2.12 (dd, *J* = 6.6, 6.9 Hz, 1 H), 1.94 (dd, *J* = 5.1, 7.8 Hz, 1 H), 1.97–2.04 (m, 1 H), 1.91 (s, 3 H), 1.90–1.40 (m, 4 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.89 (s, 9 H), –0.33 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.4, 143.9, 140.8, 135.8, 125.9, 119.0, 115.1, 59.3, 59.2, 48.9, 45.8, 38.9, 37.8, 29.6, 19.6, 19.5, 15.0. MS (EI): *m/z* calcd for $C_{17}H_{26}O_2$ $[M]^+$: 262; found: 262. HRMS (EI): *m/z* calcd for $C_{17}H_{26}O_2^+$ $[M]^+$: 262.1933; found: 262.1925.

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(21) Diol **2**: $[\alpha]_D^{24}$ –2.2 (*c* 0.51, $CHCl_3$). IR (neat): 3488, 2925, 1708, 1456, 1263, 1151, 1028 cm^{-1}. ^1H NMR (500 Hz, $CDCl_3$): δ = 6.76 (t, *J* = 6.9 Hz, 1 H), 5.87 (dt, *J* = 6.8, 15.3 Hz, 1 H), 5.56 (s, 1 H), 5.23 (dd, *J* = 6.9, 14.6 Hz, 1 H), 5.04 (ddd, *J* = 3.2, 6.0, 12.6 Hz, 1 H), 4.97 (s, 1 H), 4.81 (s, 1 H), 4.74–4.60 (m, 4 H), 4.19 (d, *J* = 5.2 Hz, 1 H), 4.05–3.96 (m, 1 H), 3.76 (m, 1 H), 3.70 (m, 1 H), 3.65 (m, 1 H), 3.35 (s, 6 H), 3.09 (br s, 1 H), 3.02 (dd, *J* = 2.1, 7.9 Hz, 1 H), 2.85 (dt, *J* = 2.1, 8.6 Hz, 1 H), 2.76–2.63 (m, 2 H), 2.33–2.22 (m, 5 H), 2.16 (m, 1 H), 2.10 (dd, *J* = 5.1, 7.8 Hz, 1 H), 1.97–1.91 (m, 2 H), 1.83 (s, 3 H), 1.82 (m, 1 H), 1.74 (s, 3 H), 1.71–1.65 (m, 1 H), 1.61–1.49 (m, 2 H), 1.43–1.36 (m, 1 H), 1.29–1.21 (m, 2 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.0, 168.4, 144.3, 142.5, 141.7, 134.2, 129.3, 128.3, 125.4, 114.7, 97.7, 97.3, 84.0, 81.2, 74.0, 66.0, 65.8, 59.1, 58.9, 56.4, 56.2, 46.8, 46.0, 41.5, 40.1, 39.2, 34.7, 31.8, 30.9, 29.8, 27.7, 19.9, 19.8, 14.7, 14.4, 12.6. ESI-MS: *m/z* calcd for $C_{36}H_{58}O_{10}$: 650; found $C_{26}H_{58}O_{10}Na^+$: 673 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{36}H_{58}O_{10}Na^+$ $[M + Na]^+$: 673.3922; found: 673.3909.

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(23) When we were preparing this manuscript and trying to deprotect the MOM group, Füstner group reported the first example of total synthesis of the amphidinolide H1 (**1**), see ref. 4b.