# Synthetic Studies toward Amphidinolide H1: Segment C14–C26

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*Received 25 August 2006*

**Abstract:** Stereoselective synthesis of the C14–C26 moiety of amphidinolide H1 is described. The key features of the approach include the convergent fragment assembly with a highly diastereoselective aldol reaction to establish the C18 stereochemistry and using commercially available chiral pool.

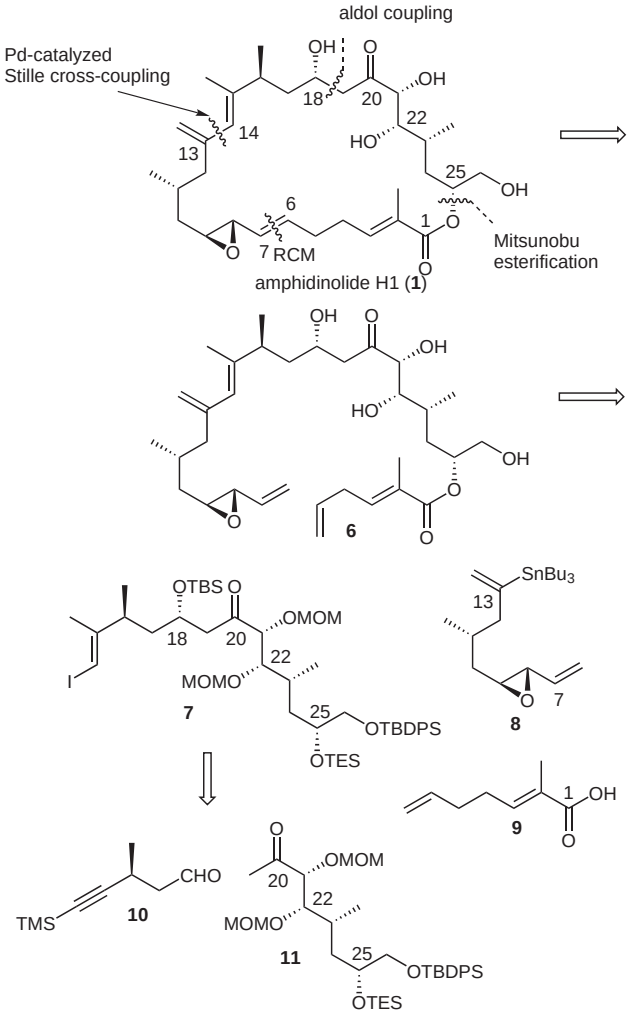
**Key words:** amphidinolide H1, macrolide, aldol reaction, Wittig reaction, dihydroxylation

A family of structurally diverse macrolides, the so-called amphidinolides, was obtained from marine dinoflagellates of the genus *Amphidinium* living in symbiosis with Okinawan acoel flatworm *Amphiscolops* spp.[1,2] Amphidinolide H1 (**1**) and its congeners H2–H5[3a] are a group of 26-membered macrolides bearing unique structural features such as an allyl epoxide or vicinally located one-carbon branches.[3b]

The gross structure of **1** was elucidated by the means of 2D NMR data, and the absolute stereochemistry was determined on the basis of X-ray diffraction analysis and degradation.[4] It exhibits extremely potent cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines, which may result not only from the characteristic groups such as *S*-*cis*-diene and the allyl epoxide but also from its unique 3D structure.[5] Due to its biological activity and challenging structure, amphidinolide H1 represents an attractive synthetic interest,[6,7] yet no total synthesis of **1** has been reported to date. Very recently, we have finished the total synthesis of amphidinolide T3 and formal synthesis of amphidinolide T4.[8b] Herein, we describe the stereoselective synthesis of the C14–C26 fragment **12** of amphidinolide H1.

As shown in Scheme 1, our initial retrosynthetic approach involves an intramolecular ring-closing metathesis (RCM) of alkene **6**, which might be obtained from intermediates **7**, **8** and **9** either via an intermolecular Stille coupling reaction, or via a Mitsunobu esterification. The C14–C26 segment **7** of the top half of amphidinolide H1 could be furnished by an aldol coupling between the aldehyde **10** and methyl ketone **11**.

The synthesis of aldehyde **10** could be achieved by a multistep sequence[9] from the known chiral alcohol **13**, which can be easily prepared either from commercially available

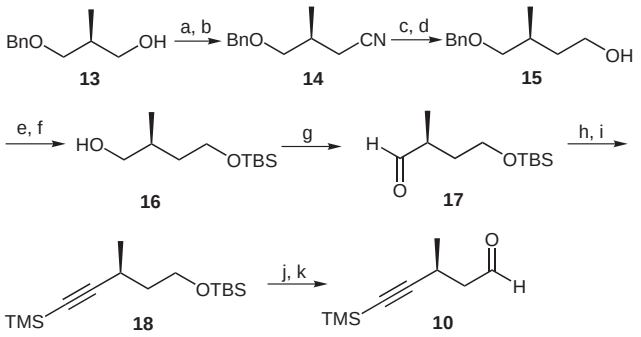



**Scheme 1** Retrosynthetic analysis of amphidinolide H1 (**1**)

methyl (*R*)-3-hydroxyl-2-methylpropionate or by the Lewis acid mediated alkylation of *N*-propionyloxazolidinone with benzyl chloromethyl ether (Scheme 2).[8]

Treatment of alcohol **13** with mesyl chloride and triethylamine in dichloromethane at 0 °C followed by displacement of the resulting mesylate with sodium cyanide in dimethyl sulfoxide at 60 °C provided cyanide **14** in 97% yield. Diisobutylaluminum hydride (DIBAL-H) reduction of cyanide **14** and subsequent treatment of the corresponding aldehyde with sodium borohydride gave the primary alcohol **15** in a good yield. After protection of the hydroxyl group of **15** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), reductive removal of the

***SYNLETT*** 2007, No. 1, pp 0087–0090
Advanced online publication: 20.12.2006
DOI: 10.1055/s-2006-956498; Art ID: W17506ST

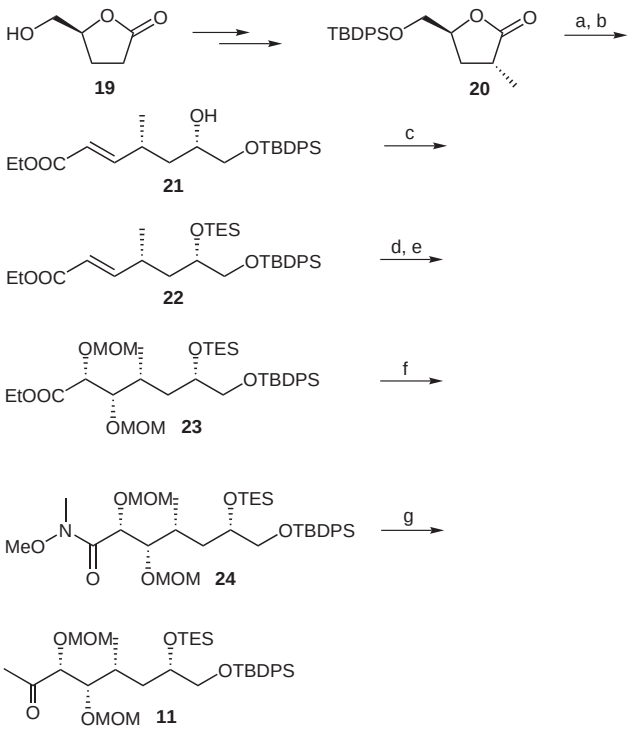



**Scheme 2** *Reagents and conditions*: (a) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C; (b) NaCN, DMSO, 60 °C, 97% over two steps; (c) DIBAL-H, $CH_2Cl_2$, 0 °C, 91%; (d) $NaBH_4$, $CH_2Cl_2$–MeOH, 0 °C–r.t., 85%; (e) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 96%; (f) Li, $NH_3$ (l), THF, –78 °C, 99%; (g) DMP, $CH_2Cl_2$, $NaHCO_3$, 84%; (h) $CBr_4$, $PPh_3$, 2,6-lutidine, $CH_2Cl_2$, 88%; (i) *n*-BuLi, TMSCl, THF, –78 °C, 97%; (j) CSA, MeOH; (k) $(COCl)_2$, DMSO, $CH_2Cl_2$, –78 °C, then $Et_3N$, –40 °C, 82% over two steps.

benzyl group in the resulting silyl ether was achieved in the presence of lithium–ammonia at –78 °C to provide **16** in 99% yield. Oxidation of **16** using the Dess–Martin periodinane followed by treatment of the corresponding aldehyde with tetrabromomethane and triphenylphosphine led to the α,α-dibromoalkene in 88% yield,[10] which was next converted into trimethylsilyl alkyne **18** (97%) using *n*-butyllithium and trimethylsilyl chloride (TMSCl) at room temperature. After selective desilylation of **18** with 10-camphorsulfonic acid (CSA) in methanol, the resulting alcohol was subjected to Swern oxidation conditions to give the desired aldehyde **10** in 82% yield.[11]

As outlined in Scheme 3, the synthesis of the C19–C26 fragment **11** was investigated using commercially available alcohol **19**,[12] which was conveniently converted into **20** by silylation and stereoselective methylation according to the published procedures.[13] DIBAL-H reduction of **15** followed by the Wittig reaction using $Ph_3P{=}CHCO_2Et$ afforded *E* olefin **21** in 94% yield in two steps. After silylation of the resulting alcohol with triethylsilyl trifluoromethanesulfonate (TESOTf), enoate **22** was then dihydroxylated with AD-mix-α*[14] in *tert*-butanol–water at 0 °C to give a diol, which in turn was protected as methoxymethyl (MOM) ether to provide ester **23** in a good yield (86% over two steps). Various conditions were screened for the formation of the Weinreb amide **24**. Aluminum reagents gave poor yields of the triethylsilyl ether **23** ($Me_3Al$, $CH_2Cl_2$, –10 °C–r.t., 11% yield). However, a solution was found by using the modified method developed by Merck (LHMDS, THF, –50 °C) which afforded the desired amide **24** in 98% yield.[15] Next, the formation of the methyl ketone **11** proceeded smoothly by treatment of **24** with methyllithium at –78 °C.[16]

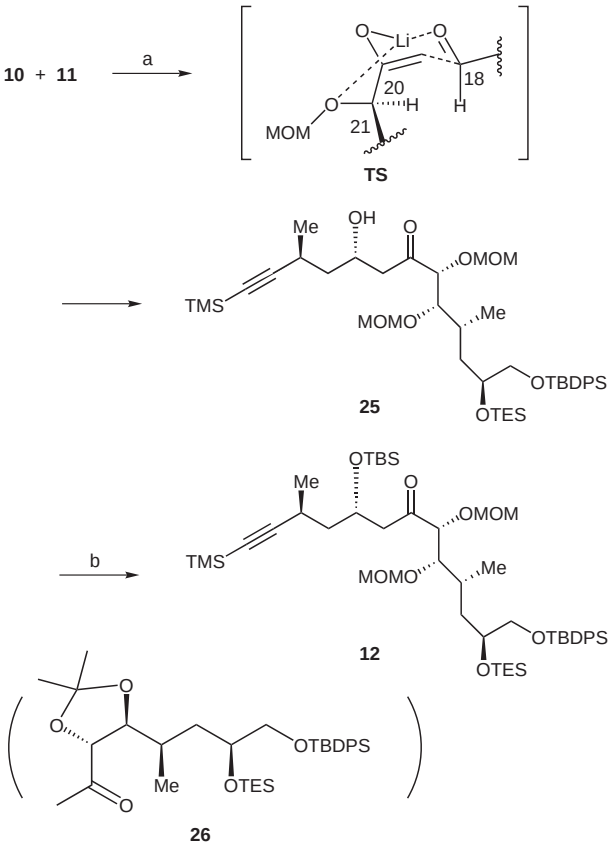
With the required two segments in hand, our subsequent design strategy called for the assembly of the aldehyde **10** and methyl ketone **11** (Scheme 4). Treatment of **11** with lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran at –78 °C followed by adding the precooled **10** led




**Scheme 3** *Reagents and conditions*: (a) DIBAL-H, $CH_2Cl_2$, –78 °C; (b) $Ph_3P{=}CHCO_2Et$, benzene, 80 °C, 94% over two steps; (c) TESOTf, 2,6-lutidine, 0 °C, 98%; (d) $(DHQ)_2PHAL$, $OsO_4{\cdot}H_2O$, $K_3Fe(CN)_6$, $K_2CO_3$, $NaHCO_3$, $MeSO_2NH_2$, *tert*-BuOH–$H_2O$; (e) MOMCl, DIPEA, TBAI, $CH_2Cl_2$, 40 °C, 86% over two steps; (f) MeON(Me)H·HCl, LHMDS, THF, –50 °C, 98%; (g) MeLi, THF, –78 °C, 98%.

to an aldol product in 63% yield with excellent diastereoselectivity (dr > 15:1), which was in contrast to the work on synthetic studies toward amphidinolide B by Pattenden's and Kobayashi's groups.[7e,i] In their efforts, non-chelating silyl protecting groups[17] were employed on C21 of the enolate. We speculated that the good selectivity at C18 might be attributed to the existence of the α-chelating MOM group on the enolate, as shown in the model **TS** on the basis of published literature.[7b,18] However, a lower selectivity (dr 5:1) occurred when methyl ketone **26** was applied in the aldol reaction with **10**. It was noteworthy that the solvent was important in this reaction and diethyl ether did not give a good result (dr 3:1). Furthermore, the enolate generated from lithium diisopropylamide in tetrahydrofuran or in diethyl ether gave poor selectivity. The stereochemistry at C18 of **25** was in accordance with that in **1** on the basis of Mosher ester analysis.[19] Finally, protection of the resulting secondary alcohol with TBSOTf provided the desired segment **12** in 97% yield.[20]

In summary, we have synthesized the C14–C26 segment **12** via a highly concise and convergent strategy in nine steps from silyl ether **20** and 46% overall yield. A highly diastereoselective aldol reaction was featured in this approach. Further investigation toward the total synthesis of amphidinolide H1 is currently underway in our laboratory.




**Scheme 4** *Reagents and conditions*: (a) **11**, LHMDS, THF, –78 °C, 20 min, then **10**, –78 °C, 2 h, 63%; (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 97%.

## Acknowledgment

We are grateful to National Natural Science Foundation of China (No. 20525208, 20532040, 20390057 and 20372072), QT program and Shanghai Natural Science Council for financial support.

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(11) Aldehyde **6**: $R_f$ 0.41 (PE–EtOAc, 20:1); $[\alpha]_D^{26}$ +4.7 (*c* = 0.70, $CHCl_3$). IR (film): 2962, 2169, 1729, 1250 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 2.1 Hz, 1 H), 2.96–3.03 (m, 1 H), 2.45–2.63 (m, 2 H), 1.23 (d, *J* = 7.2 Hz, 3 H), 0.13 (s, 9 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 201.1, 109.2, 85.6, 49.8, 21.6, 20.9, 0.1. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_{16}OSi$: 168.0970; found: 168.0972.

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(14) AD-mix-α*: $OsO_4 \cdot H_2O$ (1 mol%), $(DHQ)_2PHAL$ (2 mol%), $K_3Fe(CN)_6$ (3 equiv), $K_2CO_3$ (3 equiv), $NaHCO_3$ (3 equiv), and $MeSO_2NH_2$ (1 equiv). The reaction occurred at a significantly slower rate using commercially available AD-mix-α.

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(16) Methyl ketone **11**: $R_f$ 0.36 (PE–EtOAc, 15:1); $[\alpha]_D^{26}$ +3.1 (*c* = 0.76, $CHCl_3$). IR (film): 2955, 1717, 1030 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.65–7.68 (m, 4 H), 7.26–7.42 (m, 6 H), 4.59–4.70 (m, 4 H), 4.06 (d, *J* = 5.1 Hz, 1 H), 3.82 (m, 1 H), 3.71 (m, 1 H), 3.42 (ddd, *J* = 5.1, 10.2, 10.5 Hz, 2 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 2.18 (m, 3 H), 1.77–1.89 (m, 2 H), 1.41–1.48 (m, 1 H), 1.04 (s, 9 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 7.8 Hz, 9 H), 0.52 (q, *J* = 7.8 Hz, 6 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 208.4, 135.6, 133.5, 129.7, 127.7, 97.9, 97.4, 84.5, 81.8, 71.8, 67.9, 56.4, 56.2, 38.7, 31.4, 27.2, 26.9, 19.2, 15.6, 6.9, 5.0. HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{58}O_7Si_2Na$: 669.3605; found: 669.3613.

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(20) C14–C26 segment of **1**: $R_f$ 0.48 (PE–EtOAc, 19:1); $[\alpha]_D^{26}$ +15.6 (*c* = 1.70, $CHCl_3$). IR (film): 2956, 2163, 1719 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.65–7.67 (m, 4 H), 7.34–7.43 (m, 6 H), 4.58–4.64 (m, 4 H), 4.33–4.37 (m, 1 H), 4.13 (d, *J* = 4.2 Hz, 1 H), 3.82 (m, 1 H), 3.70 (m, 1 H), 3.51 (ddd, *J* = 5.1, 8.1, 10.2 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 2.90 (dd, *J* = 4.8, 10.8 Hz, 1 H), 2.60 (dd, *J* = 4.8, 10.8 Hz, 1 H), 2.42–2.50 (m, 1 H), 1.86 (m, 2 H), 1.54–1.65 (m, 3 H), 1.35–1.42 (m, 1 H), 1.15 (d, *J* = 9.6 Hz, 3 H), 1.04 (s, 9 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.90 (t, *J* = 7.8 Hz, 9 H), 0.85 (s, 9 H), 0.54 (q, *J* = 7.8 Hz, 6 H), 0.13 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 209.0, 135.6, 133.5, 129.6, 127.7, 111.8, 97.6, 97.0, 84.4, 84.1, 82.1, 72.0, 68.1, 66.7, 56.4, 56.2, 46.3, 44.4, 38.5, 31.8, 26.9, 25.9, 23.1, 21.1, 19.2, 18.0, 16.1, 7.0, 5.1, 0.2, –4.4, –4.6. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{50}H_{88}O_8Si_4$: 951.5498; found: 951.5449.