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Synthesis of the C7-26 Fragment of Amphidinolides G and H

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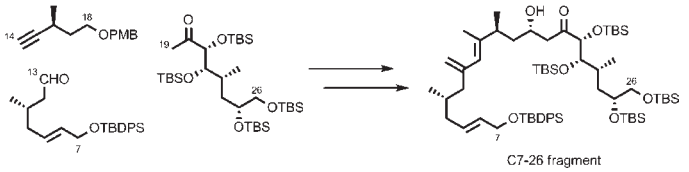
ABSTRACT



A new approach to the synthesis of the C7-26 fragment of amphidinolides G and H was developed. In the sequence, the C7-18 portion of this fragment was synthesized using an acetylide coupling protocol, while an Evans alkylation and Sharpless asymmetric dihydroxylation were employed as key steps in construction of the C19-26 subfragment. Finally, both of these units were joined by utilizing an aldol coupling reaction to produce the target C7-26 fragment in good yield.

Amphidinolides G (**1**) and H (**2**), isolated by Kobayashi and co-workers from the Okinawan flatworm *Amphiscolops* sp.,[1] possess remarkably strong cytotoxicity against L1210 murine lymphoma (IC_{50} = 5.4 ng/mL for **1** and 0.48 ng/mL for **2**) and KB human epidermoid[2] (IC_{50} = 5.9 ng/mL for **1** and 0.52 ng/mL for **2**), and **2** has the potential to activate actin polymerization by covalently linking to the actin cytoskeleton[3] (Figure 1). Both of these natural products contain allyl epoxide, *s-cis*-diene units, five hydroxyl groups, and nine stereocenters in respective 26- and 27-membered macrocyclic lactone moieties. Interestingly, amphidinolides G (**1**) and H (**2**) exist in equilibrium with each other under acidic or basic conditions.[4,6] The interesting biological activities and unique structural features of these natural products have attracted the organic synthesis community.[5] Despite this activity, only one total synthesis of these substances has been reported since the time of their isolation.[6] In a recent effort, we have developed a new route for the preparation of the C7-26 fragment of these targets. Observations made in this study are described below.

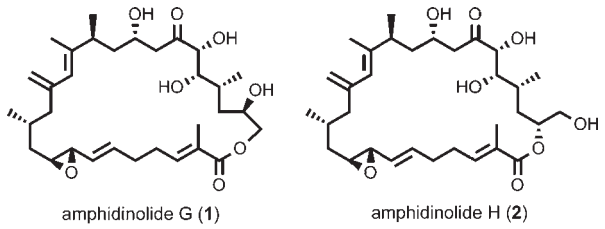


Figure 1. Structure of amphidinolides G (**1**) and H (**2**).

On the basis of a strategy represented in the retrosynthetic analysis displayed in Scheme 1, amphidinolide G (**1**) would be generated from the alcohol **3** through a sequence that utilizes esterification with an appropriate unsaturated

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(2) Kobayashi, J.; Shimbo, K.; Sato, M.; Tsuda, M. *J. Org. Chem.* **2002**, *67*, 6585–6592.

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(4) Kobayashi, J.; Shimbo, K.; Sato, M.; Shiro, M.; Tsuda, M. *Org. Lett.* **2000**, *2*, 2805–2807.

(5) For synthetic studies aimed at amphidinolides G and H, see: (a) Petri, A. F.; Schneekloth, J. S.; Mandal, A. K.; Crews, C. M. *Org. Lett.* **2007**, *9*, 3001–3004. (b) Deng, L.; Ma, Z.; Zhang, Y.; Zhao, G. *Synlett* **2007**, 87–90. (c) Deng, L.; Ma, Z.; Zhao, G. *Synlett* **2008**, 728–732. (d) Formentin, P.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2938–2942. (e) Liesener, F. P.; Kalesse, M. *Synlett* **2005**, 2236–2238. (f) Liesener, F. P.; Jannsen, U.; Kalesse, M. *Synthesis* **2006**, 2590–2602. (g) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775–7778. (h) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 9109–9112.

(6) Fürstner, A.; Bouchez, L. C.; Funel, J.; Liepins, V.; Porée, F.; Gilmour, R.; Beaufils, F.; Tamiya, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9265–9270.

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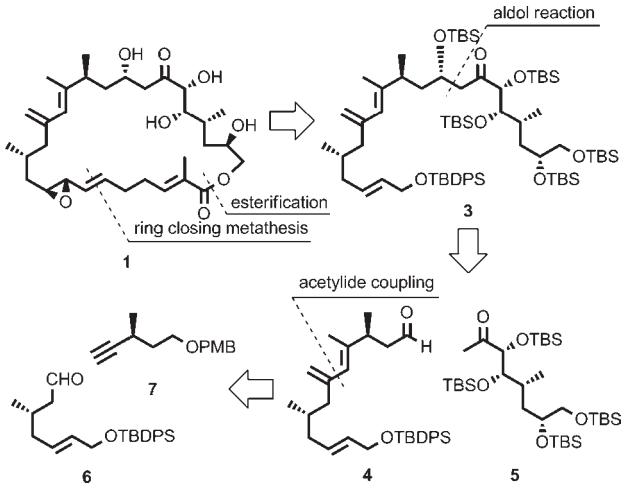
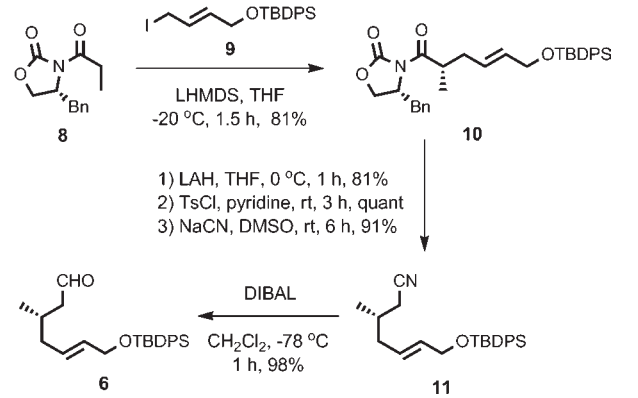
Scheme 1. Retrosynthetic Analysis of Amphidinolide G (**1**)



carboxylic acid and ring closing metathesis as key steps. In addition, owing to its lability under acidic and basic conditions, the allylic epoxide moiety in the target would be introduced by employing a late-stage Sharpless epoxidation. We envisaged that ketone **3**, corresponding to the C7-26 fragment of **1**, would serve as the key synthetic intermediate in this approach and would be prepared by the aldol reaction of aldehyde **4** with methyl ketone **5**, the former being derived from an acetylide coupling between aldehyde **6** and acetylene **7**.

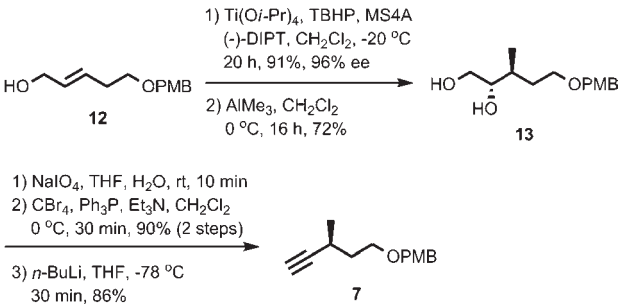
Synthesis of the aldehyde segment **6** was initiated by employing Evans alkylation of the known acylated oxazolidinone **8** with allyl iodide **9**. This process formed adduct **10** in 81% yield as a single diastereomer (Scheme 2).[7]

Scheme 2. Synthesis of C7-13 Fragment (**6**)



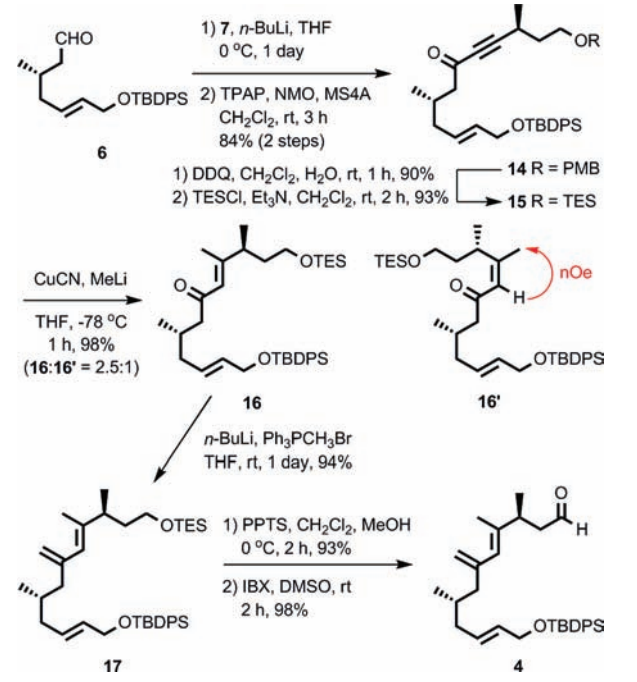
Reductive removal of the chiral auxiliary in this substance followed by the tosylation of the resulting alcohol and cyanide substitution gave nitrile **11**, which upon DIBAL reduction at −78 °C furnished aldehyde **6**.

Scheme 3. Synthesis of C14-18 Fragment (**7**)



The terminal acetylene coupling partner **7** was produced from the previously described alcohol **12**[8] (Scheme 3). Sharpless asymmetric epoxidation of **12** proceeded smoothly to afford the corresponding epoxy alcohol with 96% ee. Treatment of this substance with $AlMe_3$ led to generation of diol **13**, which was cleaved using $NaIO_4$ to produce the corresponding aldehyde, which was then converted into acetylene **7** (77% yield, 3 steps) by utilizing the Corey−Fuchs protocol.[9]

Scheme 4. Synthesis of C7-18 Fragment (**4**)



The coupling reaction between alkyne **7** and aldehyde **6** was successfully performed using *n*-BuLi to generate the key lithium acetylide. TPAP oxidation of the resulting propargylic alcohol gave the α,β-unsaturated ketone **14** in 84% yield (2 steps) (Scheme 4). Cleavage of the PMB group from **14** with DDQ produced the corresponding

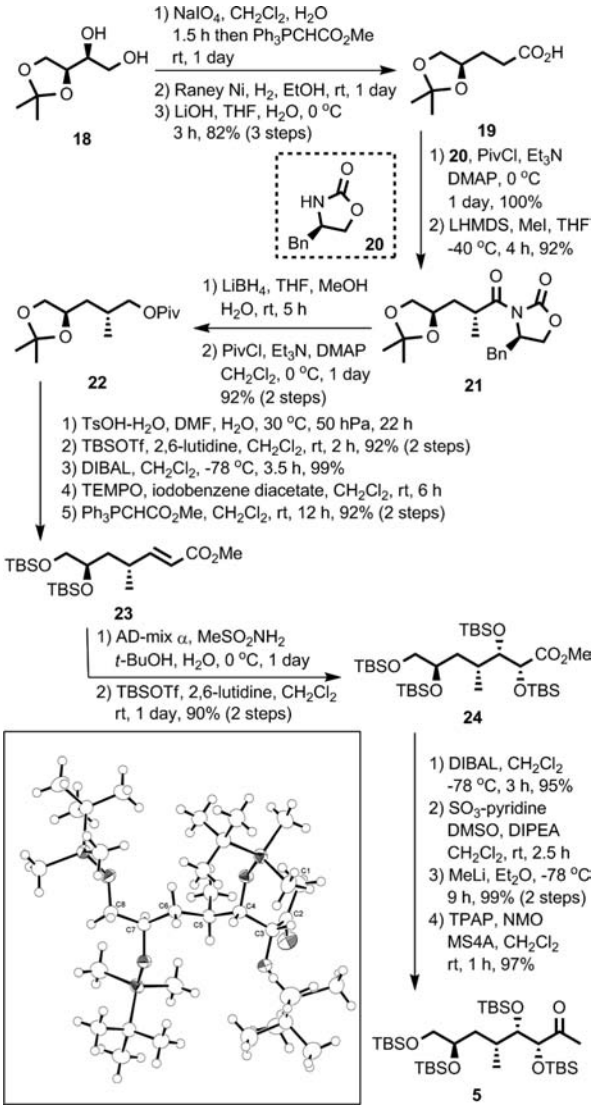
(7) Shindo, M.; Sugioka, T.; Umaba, Y.; Shishido, K. *Tetrahedron Lett*. **2004**, *45*, 8863–8866.

(8) Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1–20.

(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, *13*, 3769–3772.

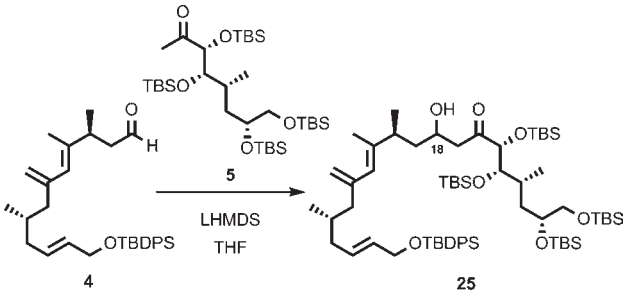
primary alcohol which, on treatment with TESCl and Et_3N, afforded ketone **15**. Treatment of **15** with the Gilman reagent promoted conjugate addition, leading to formation of the desired (*E*)-enone **16** in 98% yield with a moderate *E*:*Z* selectivity (2.5:1). The isomers **16** and **16′** were easily separated using flash silica gel column chromatography. The enone was then converted by Wittig olefination[10] to triene **17**, whose *s-cis*-diene geometry was assigned by NOE methods. Removal of the TES group from **17**, employing PPTS at 0 °C, followed by IBX oxidation of the derived alcohol provided aldehyde **4**.

Scheme 5. Synthesis of C19-26 Fragment (**5**)



The ketone **5** partner, whose aldol reaction with aldehyde **4** serves as the key step in the approach to the C7-26 fragment of amphidinolide G (**1**), was prepared by a route starting with the known diol **18**[11] (Scheme 5). Oxidative cleavage of the diol moiety in **18** followed by Wittig olefination to introduce the acrylate moiety, hydrogenation, and ester hydrolysis gave the carboxylic acid **19**. The Wittig olefination process was carried out using the crude aldehyde derived from **18** to avoid undesired epimerization. Stereoselective methylation of **21** was accomplished by using the chiral auxiliary directed Evans protocol. Reductive removal of the chiral auxiliary from product **21** gave the corresponding alcohol which, on treatment with PivCl and DMAP, afforded pivaloate ester **22**. Removal of the acetonide from **22** followed by protection of the resulting diol as the bis-TBS ether, DIBAL reduction, TEMPO oxidation, and Wittig olefination gave the acrylate ester **23**. Sharpless asymmetric dihydroxylation of this intermediate afforded a single diastereomer of the corresponding diol, which was treated with TBSOTf and 2,6-lutidine to produce the fully silyl ether protected tetraol **24**. DIBAL reduction of the ester moiety in **24**, followed by Parikh−Doering oxidation, MeLi addition, and TPAP oxidation led to the desired methyl ketone **5**, whose stereochemistry was confirmed by using X-ray crystallographic analysis.

Table 1. Aldol Reaction between **4** and **5**



entry	additive	temp (°C)[a]	yield (%)[b]	selectivity (*S*/*R*)[c]
1	none	−78	44	1:4.1
2	none	−40	54	1:3.5
3	none	−20	74	1:1.5
4	none	−10	74	1.3:1
5	none	0	50	1.2:1
6	TMEDA	−40	36	1:2.8

[a] Compound **4** was added to the enolate derived from **5** in THF at the temperature. The enolate was obtained by treatment of **5** with a base at room temperature. [b] Combined yield of (*S*)-**25** and (*R*)-**25**. [c] The ratio was determined by ^{1}H NMR spectoscopy.

With the requisite fragments in hand, the key aldol coupling process between **4** and **5** was explored (Table 1). Although ketone **5** was readily deprotonated using LHMDS at room temperature, treatment of the derived lithium

(10) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 571–572.
(11) Abushanab, E.; Raymond, P. P. *J. Org. Chem.* **1988**, *53*, 2598–2602.
(12) Diastereomers (*R*)-**25** and (*S*)-**25** were separated by using silica gel column chromatography (WAKO gel C-300).
(13) The O-PMB (ref 6) or O-MOM (refs 5b and 5c) substituents at C21 are known to induce the formation of *S*-configuration at C18 of **25** via the strong 1,4-*anti* chelation effect. However, deprotection of these groups at the final stage of the synthesis was troublesome owing to the lability of the *s-cis*-diene and allyl epoxide units under the standard deprotective conditions (DDQ, CAN for the O-PMB: acidic conditions such as BF_3OEt_2 for the O-MOM).

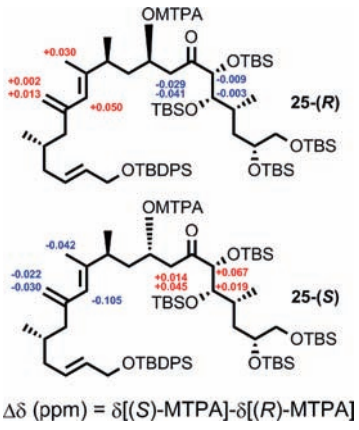


Figure 2. Data for the assignment of the C18 configuration of **25**.

enolate with aldehyde **4** at −78 °C provided the undesired diastereomer (S/R = 1:4.1, entry 1) of aldol product **25** in 44% yield.[12] The absolute configuration at C18 of **25** was assigned by employing a modification of the Mosher method[14] (Figure 2). Interestingly, temperature plays an important role in both the yield and diastereoselectivity of this process (entries 2−4). For example, aldol reaction of **4** with **5**, carried out at −10 °C, afforded **25** in 74% yield with moderate stereoselectivity[13] (S/R = 1.3:1, entry 4). In contrast, reaction at temperatures above 0 °C led to formation of the corresponding enone in low yield (entry 5). In addition, the use of TMEDA as an additive resulted in a reduced yield (entry 6). The combined results show that the desired diastereomer of the target C7-26 fragment **25** of amphidinolide G can be generated in a modest yield and diastereoselectivity.

In conclusion, a synthesis of the C7-26 fragment of **1** and **2** has been accomplished. The C7-18 fragment (**4**) was produced by employing an acetylide coupling as a key step. Furthermore, we demonstrated that the *s-cis*-diene moiety of **1** and **2** could be constructed through a 1,4-addition and a Wittig reaction. Finally, we succeeded in synthesizing the desired aldol (*S*)-**25** as a major product by aldol coupling between **4** and **5**. Further efforts toward total synthesis of amphidinolides G and H are currently continuing in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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