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Synthesis of the C3–C18 Fragment of Amphidinolides G and H

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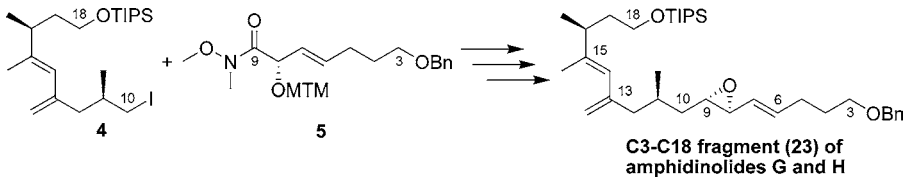
ABSTRACT



A synthesis of an amphidinolides G and H C3–C18 subunits is reported. The C10–C18 segment 4 was prepared by a Negishi cross-coupling, whereas the synthesis of the C3–C9 fragment 5 employed an asymmetric cyanosilylation as the key step. The two segments were coupled by lithiation of iodide 4 and trapping of the anion with amide 5. The allylic epoxide moiety could be synthesized from the protected *anti*- mesylate 22.

The amphidinolides are a structurally diverse group of bioactive secondary metabolites isolated from the symbiotic marine dinoflagellate *Amphidinium* sp.[1] Amphidinolides G (**1**) and H (**2**) are polyketide-based 27- and 26-membered macrolides, respectively, that were first isolated in 1991 by Kobayashi et al.[2] These two compounds putatively arise from the same seco acid. The gross structures of **1** and **2** have been elucidated primarily by means of 2D NMR data, whereas the absolute stereochemistry was determined on the basis of X-ray diffraction analysis and degradation[3] (Figure 1).

Both amphidinolides G (**1**) and H (**2**) were shown to be among the most potent cytotoxic amphidinolides. Whereas amphidinolide H (**2**) exhibits extremely potent cytotoxic activity against L1210 murine lymphoma and KB epidermoid carcinoma cells (IC_{50} = 0.00048 and 0.00052 μg/mL, respectively), amphidinolide G (**1**) showed approximately a 10-fold decrease in activity with IC_{50} values of 0.0054 and 0.0046 μg/mL, respectively.[4] Amphidinolide H (**2**) has been implicated in binding to actin subdomain 4 as a potential mode of action.[5]

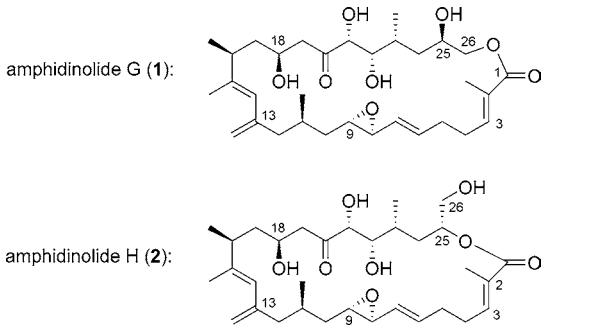


Figure 1. Amphidinolides G (**1**) and H (**2**).

Because of their remarkable biological activity and challenging structure, amphidinolides G and H represent an attractive target for synthetic efforts. Although several

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(1) For reviews, see: (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753. (b) Chakraborty, T.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131. (c) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337. (d) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (e) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451.

(2) Kobayashi, J.; Shigemori, H.; Ishibashi, M.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Org. Chem.* **1991**, *56*, 5221.

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

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

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syntheses of fragments of amphidinolides G and H and the structurally related amphidinolide B have been published,[1,6,7] to our knowledge no total synthesis of either of these amphidinolides has been accomplished so far.

Our proposed synthetic route to amphidinolide H (**2**) divides the structure into the three major fragments **3**, **4**, and **5**, allowing a convergent assembly of the molecule (Figure 2). To couple these fragments, we could establish the bond

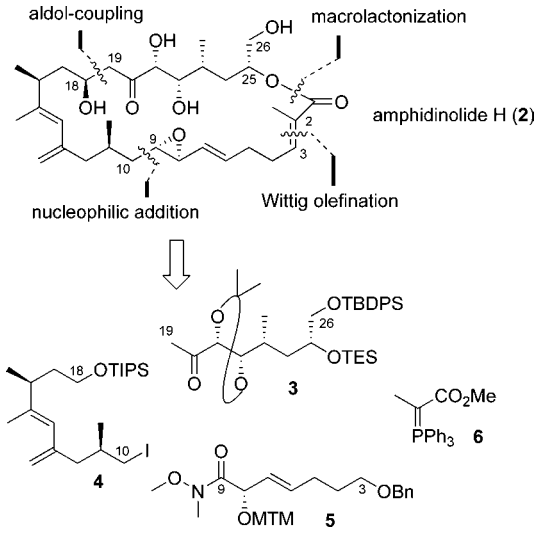
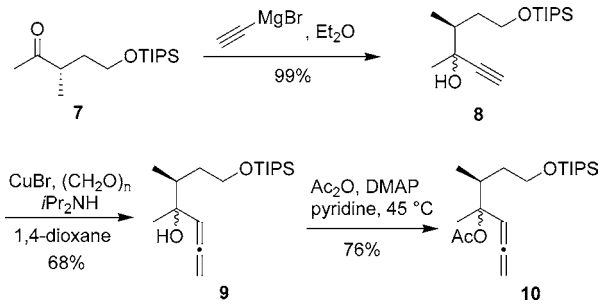


Figure 2. Retrosynthetic analysis of amphidinolide H (**2**).

between C9 and C10 by nucleophilic addition of an alkyllithium species derived from fragment **4** into Weinreb amide **5**. We propose an aldol coupling to construct the C18−C19 bond and a Wittig olefination with commercially available ylide **6** across C2 and C3. Finally, a macrolactonization should complete the carbon skeleton of amphidinolide G (**1**) or amphidinolide H (**2**).

Our synthetic efforts toward the C10−C18 fragment **4** began with ketone **7**, which was prepared from (−)-pseudoephedrine propionamide under the conditions developed by Myers[8] (Scheme 1). Ketone **7** was further elaborated to propargylic alcohol **8** (as a 1:1 mixture of diastereomers)

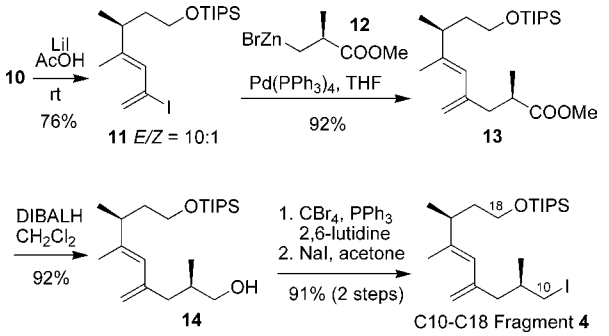
Scheme 1. Synthesis of Allenic Acetate **10**



by treatment with ethynylmagnesium bromide. Alcohol **8** was then homologated under Crabbé's conditions[9] to form allenol **9** in 68% yield. Acetylation of **9** was accomplished by treatment with Ac_2O and DMAP in pyridine at 45 °C to provide allenic acetate **10** in 76% yield.

Having established a synthetic route to access the allenic acetate **10**, we turned our attention to the synthesis of the 1,3-diene moiety. Our laboratory has previously demonstrated that the (*E*)-1,3-diene moiety of amphidinolide B can be synthesized from an allenic acetate precursor.[7f,10] When the allenic acetate **10** was treated under the reaction conditions previously described by Bäckvall[11] (LiI, $Pd(OAc)_2$, AcOH, 40 °C), the iodide-mediated S_N2' reaction gave the vinyl iodide **11** in 80% yield and a low *E*/*Z*-selectivity of 2:1. We were pleased to find that the iodide **11** could be obtained in 76% yield and an *E*/*Z*-ratio of 10:1 by performing the reaction in the absence of Pd catalyst at room temperature (Scheme 2). Moving forward, we next concentrated our

Scheme 2. Synthesis of the C10−C18 Fragment **4**



efforts to establish the C12−C13 bond by reacting vinyl iodide **11** with a suitable coupling partner. Gratifyingly, iodide **11** could be reacted with the commercially available organozinc species **12** under Negishi-type cross-coupling

(5) (a) Usui, T.; Kazami, S.; Dohmae, N.; Mashimo, Y.; Kondo, H.; Tsuda, M.; Terasaki, A. G.; Ohashi, K.; Kobayashi, J.; Osada, H. *Chem. Biol.* **2004**, *11*, 1269. (b) Saito, S.-Y.; Feng, J.; Kira, A.; Kobayashi, J.; Ohizumi, Y. *Biochem. Biophys. Res. Commun.* **2004**, *320*, 961.

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(8) (a) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(9) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.

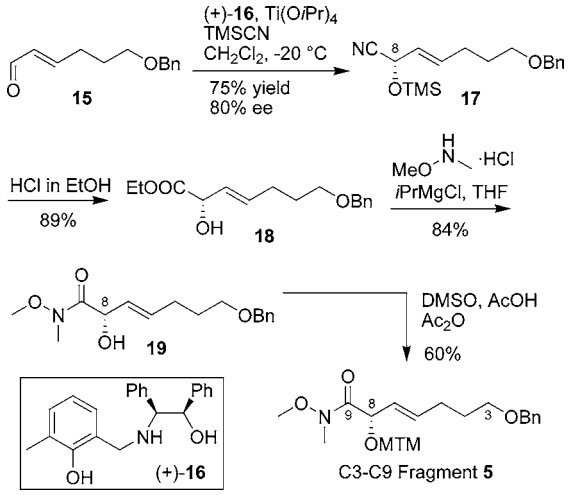
(10) Schneekloth, J. S., Jr.; Pucheault, M.; Crews, C. M. *Eur. J. Org. Chem.* **2007**, 40.

(11) Horváth, A.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120.

conditions[12] to give the ester **13** in 92% yield. No isomerization of the diene moiety was observed under these reaction conditions. Ester **13** could then be converted into alcohol **14** by reduction with DIBALH (92%). It was determined that alcohol **14** decomposes to an uncharacterized mixture of side products upon exposure to silica gel or even neutralized silica gel. Therefore, the crude alcohol **14** was carried forward without further purification. Functionalization of alcohol **14** to the iodide **4** proved to be nontrivial. All attempts to convert alcohol **14** directly to iodide **4** left the starting material unchanged or resulted in decomposition of the substrate.[13] Therefore, alcohol **14** was brominated (CBr_4, PPh_3, 2,6-lutidine, 99%) and a subsequent Finkelstein reaction (NaI, acetone, Δ) introduced the iodine in excellent yield (92%) and furnished the C10−C18 fragment **4**. Alkyl iodide **4** could be stored at −20 °C for 3 months without any noticeable decomposition.

We proposed to synthesize the C3−C9 fragment **5** via an asymmetric cyanosilylation of known aldehyde **15**[14] as key step. In our initial attemps, we investigated the cyanosilylation method developed by Uang[15] (which left the aldehyde **15** unchanged) and the method of Pu,[16] which gave the protected cyanohydrin **17** in 30% yield and 69% ee. We were pleased to find that we could access the TMS-protected cyanohydrin **17** in 75% chemical yield and 80% ee[17] by employing the chiral ligand (+)-**16** and Ti(O*i*Pr)$_4$ as described by Feng and co-workers[18] (Scheme 3). Exposure of **17** to HCl in

Scheme 3. Synthesis of the C3−C9 Fragment **5**



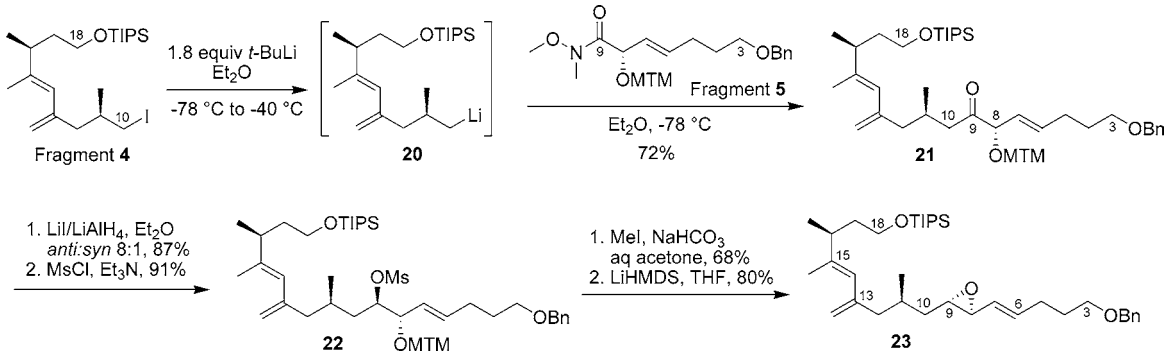
ethanol produced the α-hydroxyester **18** in 89% yield. At this stage, the stereochemistry of the C8-OH group was assigned by using the modified Mosher method,[19] which revealed the (*S*)-configuration of α-hydroxyester **18**. Amidation of ester **18** using the Merck procedure[20] ((MeO)MeNH·HCl, *i*PrMgCl) afforded Weinreb amide **19** in 84% yield.

The choice of protecting group for the hydroxy function at C8 was crucial. As it was necessary to utilize a chelating protecting group, initial studies with a PMB ether or a MOM ether were carried out (not shown). Unfortunately, later substrates containing the 1,3-diene unit of amphidinolides G and H were prone to decomposition upon treatment with DDQ or under acidic conditions, presumably by way of isomerization. In order to circumvent this issue, we chose to protect the C8 hydroxy function of **19** as an MTM (methylthiomethyl) ether[21] (DMSO, AcOH, Ac_2O, 60%), thus completing the synthesis of the C3−C9 fragment **5**.

With both fragments **4** and **5** securely in hand, we envisioned a nucleophilic addition into a Weinreb amide as the key coupling step to combine the two fragments. The lithium-halogen exchange to convert the alkyl iodide **4** to the alkyllithium species **20** proved to be a challenging transformation. In our initial experiments, we performed the lithium-halogen exchange of iodide **4** using the standard protocol,[22] which involves treatment of **4** with 2.2 equiv of *t*-BuLi at −78 °C and subsequent stirring at room temperature for 1 h to decompose excess *t*-BuLi. Under these conditions, the lithiation was found to be lacking reproducibility, and the yield of alkyllithium species **20** was usually <40%.[23] The low yields of **20** could potentially be caused by an intramolecular cyclization of the alkyllithium moiety into the 1,3-diene system, as such cyclizations are known to occur at room temperature.[24] Since the cyclization of unsaturated organolithiums can be suppressed at low temperatures, we were able to circumvent this problem by modifying the lithiation protocol.[25] When we treated iodide **4** with 1.8 equiv of *t*-BuLi at −78 °C and stirred the reaction for 10 min at −40 °C, lithium halogen exchange to **20** occurred smoothly and subsequent coupling with Weinreb amide **5** at −78 °C yielded the ketone **21** in 72% yield[26] (Scheme 4). The chelation-controlled reduction of ketone **21** (LiI/$LiAlH_4$, Et_2O, *anti*:*syn* 8:1) provided the *anti* alcohol in 87% yield as a single diastereomer after flash chromatography.[27] Mesylation of the secondary alcohol (MsCl, Et_3N, rt) afforded

(12) For a recent review on Negishi-type couplings, see: Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71.
(13) Other conditions explored were PPh3/I2/imidazole; PPh3/CI4; NaI/heat; and MsCl/NaI.
(14) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971.
(15) Uang, B. J.; Fu, I. P.; Hwang, C. D.; Chang, C. W.; Yang, C. T.; Hwang, D. R. *Tetrahedron* **2004**, *60*, 10479.
(16) Qin, Y. C.; Liu, L.; Pu, L. *Org. Lett.* **2005**, *7*, 2381.
(17) The enantiomeric excess of this reaction was determined by Mosher ester analysis of the α-hydroxyester **18**.
(18) Li, Y.; He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* **2004**, *69*, 7910.
(19) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(20) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(21) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.
(22) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.
(23) The yield of alkyllithium species **20** was determined by trapping **20** with amide **5** and isolation of the ketone **21** thus formed.
(24) For reviews about the cyclization of usaturated organolithiums, see: (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: New York, New York, 2002; Vol. 3, pp 293−335. (b) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59.
(25) Bailey, W. F.; Jiang, X. *Tetrahedron* **2005**, *61*, 3183.
(26) Because the amide **5** had an ee of 80%, the coupling yielded ~10% of the (8*R*)-epimer of ketone **21**, which could be separated by column chromatography at this stage.
(27) The relative stereochemistry was confirmed after converting the alcohol into an acetonide by NOESY NMR spectroscopy (see Supporting Information).

Scheme 4. Coupling of Fragment **4** with Fragment **5** and Completion of the C3−C18 Subunit **23**



22 in 91% yield. MTM deprotection was accomplished under mild alkylating conditions (MeI, $NaHCO_3$, aqueous acetone, 68%), and subsequent treatment of the hydroxy mesylate with LiHMDS afforded the allylic epoxide **23** in 80% yield. Epoxide **23** corresponds to the fully functionalized C3−C18 fragment of amphidinolides G (**1**) and H (**2**).

In summary, we have described an efficient synthetic route to the C3−C18 subunit **23** of amphidinolides G and H. Our studies demonstrate that the 1,3-diene moiety of these natural products can be assembled by an S_N2' reaction of an allenic acetate **10**. We have also demonstrated that a Negishi-type cross-coupling between a vinyl iodide **11** and an alkylzinc species **12** can be employed to assemble the C12−C13 bond. The two advanced fragments **4** and **5** could be combined to ketone **21** by a lithiation/nucleophilic addition sequence. Furthermore, we have shown that the allylic epoxide moiety of amphidinolides G (**1**) and H (**2**) can be effectively synthesized from the protected *anti* mesylate **22**. With the effective assembly of the 1,3-diene moiety and the allylic epoxide, two important characteristic structural features of amphidinolides G and H have been synthesized successfully. Efforts toward the eventual total synthesis of **2** are currently being pursued in our laboratory.

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

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