ORGANIC LETTERS

2000
Vol. 2, No. 7
945−948

Total Synthesis of (−)-Amphidinolide P

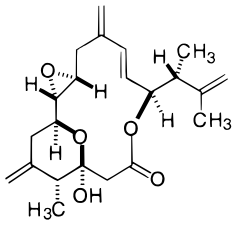
David R. Williams,* Brian J. Myers, and Liang Mi

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405-7102

williamd@indiana.edu

Received January 31, 2000

ABSTRACT



(−)-Amphidinolide P

The convergent enantiocontrolled total synthesis of the 15-membered macrolactone (−)-amphidinolide P is reported. Key transformations include a Sakurai allylation, a Stille coupling for the formation of a fully functionalized acyclic precursor, and intramolecular transesterification.

The amphidinolides are a family of structurally related cytotoxic natural products isolated from strains of microscopic marine dinoflagellates.[1] In initial studies, these metabolites have shown extremely potent in vitro antitumor activity in NCI screens.[2] Furthermore, caribenolide I,[3] a metabolite that is closely related to amphidinolide N,[2] has displayed promising in vivo activity against murine tumor P388,[3] and amphidinolide B[4] has also been shown to initiate rabbit skeletal actomyosin ATPase activity. Although culturing of the dinoflagellates is currently underway by Shimzu using 15 000 L tanks,[5] the isolated yields of individual amphidinolides are extremely low. Because of their diverse structural features, notable biological activity, and limited availability, the amphidinolides represent attractive targets for total synthesis. Several synthetic strategies have been reported,[6] and to date, the total syntheses of two amphidinolides, J[7] and K,[8] have been communicated. Our continuing efforts have focused on amphidinolide P (**1**), the relative configuration of which was deduced using 2D-NMR experiments and molecular modeling studies.[9] Herein, we report the first total synthesis of (−)-amphidinolide P (**1**), the enantiomer of the natural product, utilizing a highly efficient, convergent approach. Our synthesis affirms the relative stereochemistry and establishes the absolute configuration of the natural macrolide.

Our retrosynthetic analysis of **1** recognized bond disconnections, which would provide for macrolactonization, and installation of the $C_{11}-C_{12}$ diene as late stage events. This strategy suggested alkenes **2** and **3** as fully functionalized

(1) (a) For reviews on isolation of the amphidinolides, see: Kobayashi, J. In *Comprehensive Natural Products Chemistry*; Mori, K., Ed.; Elsevier: New York, 1999; Vol. 8, pp 619−634. (b) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543−572.

(2) Ishibashi, M.; Yamaguchi, N.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun*. **1994**, 1455−1456. Amphidinolide N displays antitumor potency (IC50 0.05 nM) at levels similar to those reported for the spongistatins.

(3) Bauer, I.; Maranda, L.; Young, K. A.; Shimizu, Y.; Fairchild, C.; Cornell, L.; MacBeth, J.; Huang, S. *J. Org. Chem*. **1995**, *60*, 1084−1086. We postulate that caribenolide I is a metabolite, which may correspond to the cyclodehydration product arising from amphidinolide N (ref 2).

(4) Matsunaga, K.; Nakatani, K.; Ishibashi, M.; Kobayashi, J.; Ohizumi, Y. *Biochim. Biophys. Acta* **1998**, *1427*, 24−32.

(5) May, M. *Environ. Health Perspect.* **1998**, *106*, A284−A285.

(6) (a) For synthetic studies directed toward the amphidinolides, see: Williams, D. R.; Meyer, K. G. *Org. Lett.* **1999**, *1*, 1303−1305. (b) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 573−575. (c) Terrell, L. R.; Ward, J. S., III; Maleczka, R. E., Jr. *Tetrahedron Lett*. **1999**, *40*, 3097−3100. (d) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1163−1166. (e) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2275−2278. (f) Chakraborty, T.; Thippeswamy, D. *Synlett* **1999**, 150−152. (g) Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett*. **1998**, *39*, 703−706. (h) Chakraborty, T. K.; Das, S. *Chem. Lett*. **2000**, 80−81.

(7) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc*. **1998**, *120*, 11198−11199.

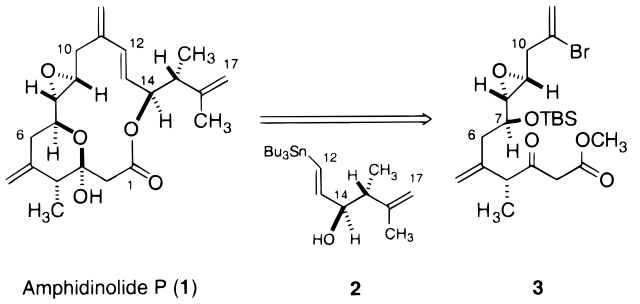
(8) Williams, D. R.; Meyer, K. G. Total Synthesis of (+)-Amphidinolide K. In *Abstracts of Papers*, 218th National Meeting of the American Chemical Society, 1999; American Chemical Society: Washington, DC, 1999; p 578-ORGN.

(9) Ishibashi, M.; Takahashi, M.; Kobayashi, J. *J. Org. Chem*. **1995**, *60*, 6062−6066.

10.1021/ol0000197 CCC: $19.00
Published on Web 03/17/2000

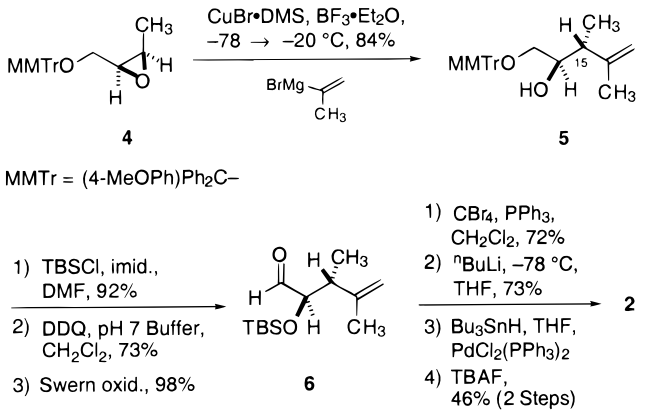
components of a Stille coupling process (Scheme 1). Further inspection of the β-keto ester **3** focused our attention on formation of the C_6-C_7 bond via a nucleophilic allylation reaction.

Scheme 1



Stannane **2** was prepared from optically active epoxide **4**[10] in eight steps (Scheme 2). Thus, a Lewis acid promoted regioselective opening of oxirane **4** provided the desired C_{14}

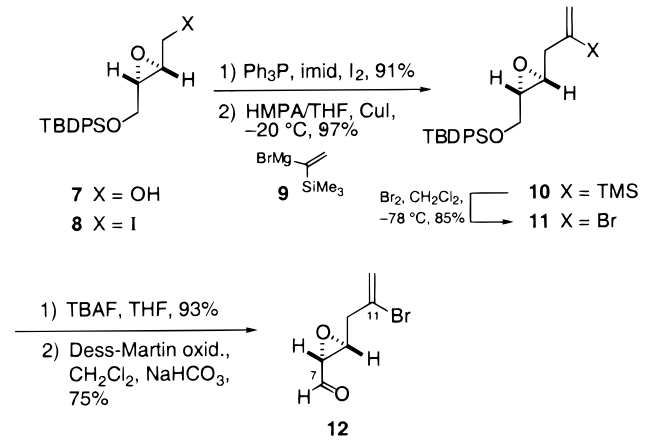
Scheme 2



secondary alcohol while establishing the C_{15} stereocenter. The resulting alcohol was protected as a *tert*-butyldimethylsilyl ether. The *p*-methoxytrityl group (MMTr)[11] in **4** served a 2-fold purpose in this reaction sequence. First, it was used to sterically impede nucleophilic attack at the C2 position, thus improving the regioselectivity in formation of **5**. Second, it provided for deprotection under neutral conditions in the presence of the secondary silyl ether, which was necessary because the use of mildly acidic or basic conditions led to substantial quantities of silyl migration and diol products.[12] The primary alcohol was oxidized to aldehyde **6** using the Swern procedure[13] with no evidence of epimerization. Subsequent transformation of **6** using the Corey−Fuchs protocol[14] provided the corresponding alkyne, which was subjected to palladium-catalyzed hydrostannylation[15] of the alkyne and was followed by removal of the silyl protecting group to give the desired (*E*)-vinylstannane **2** (Scheme 2).

Scheme 3 illustrates the straightforward preparation of the appropriately functionalized coupling partner, aldehyde **12**,

Scheme 3



for further development of the hemiketal of **1** as well as diene formation. Thus, the readily available optically active epoxy alcohol **7**[16] was converted to the corresponding iodide (**8**), and subsequent copper-catalyzed coupling with Grignard reagent **9** gave vinylsilane **10**[17] without causing elimination of **8** to the corresponding allylic alcohol or isomerization of **10** to the corresponding dienol. Conversion to the vinylic bromide **11**,[18] and removal of the silyl ether followed by oxidation with the Dess−Martin periodinane,[19] provided aldehyde **12** (Scheme 3).

The Sakurai[20] reaction of aldehyde **12** and allylsilane **13**[21] provided for the facile formation of the C_6-C_7 bond using

(10) Epoxide **4** is available in a one-pot Sharpless epoxidation and protection sequence in 82% ee. See: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765−5780.

(11) Khorana, H. G.; Goldberg, H. I.; Rammler, D. H.; Smith, M. *J. Am. Chem. Soc*. **1962**, *84*, 430−440.

(12) Although DDQ has been used for removal of acetal and PMB ether protecting groups, removal of the MMTr protecting group using DDQ has not been previously utilized to the best of our knowledge. See: (a) Oku, A.; Kinugasa, M.; Kamada, T. *Chem, Lett*. **1993**, 165−168. (b) Tanemura, K.; Nishida, Y.; Suzuki, T.; Satsumabayashi. K.; Horaguchi, T. *J. Chem. Res., Synop*. **1999**, 40−41. (c) Tanemura, K.; Suzuki, T.; Horaguchi, T. *Bull. Chem. Soc. Jpn*. **1994**, *67*, 290−292. (d) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915−917.

(13) Mancuso, A. J.; Haung, S.-L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480−2482.

(14) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769−3772.

(15) Zhang, H. X.; Gruibé, F.; Balavoine, G. *J. Org. Chem*. **1990**, *55*, 1857−1867.

(16) Epoxy alcohol **7** was prepared from 1,4-butyne diol in three steps (91% ee). See: Total Synthesis of (+)-Breynolide A. Jass, P. A. Ph.D. Thesis, Indiana University, 1994. Also see ref 10.

(17) Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett*. **1984**, *25*, 2069−2072.

(18) Miller, R. B.; McGarvey, G. *J. Org. Chem*. **1979**, *44*, 4624−4633.

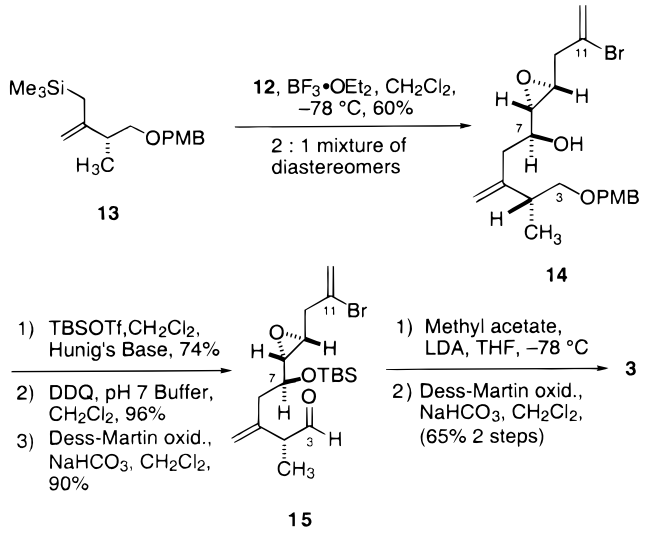
(19) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277−7278. (b) Ireland, R. E.; Liu, L. *J. Org. Chem*. **1993**, *58*, 2899.

(20) (a) Sakurai, H.; Hosomi, A. *Tetrahedron Lett*. **1976**, *16*, 1295−1298. (b) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett*. **1976**, 941−942.

(21) For the synthesis of the benzyl derivative of allylsilane **13**, see: (a) Bunnelle, W. H.; Narayanan, B. A. *Org. Synth*. **1990**, *69*, 89−95 (b) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2738−2741. (c) Mickelson, T. J.; Koviach, J. L.; Forsyth, C. J. *J. Org. Chem*. **1996**, *61*, 9617−9620.

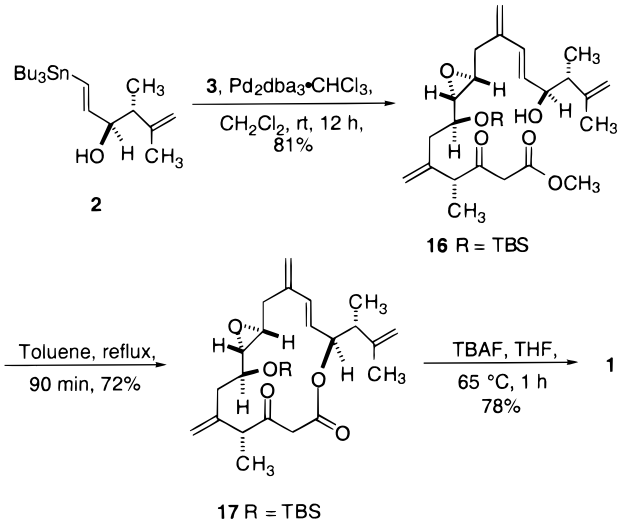
boron trifluoride etherate, which resulted in a 2:1 mixture of separable alcohol C_7 diastereomers. The desired alcohol **14** was determined to be the major diastereomer resulting from Felkin−Ahn addition.[22] The minor isomer was converted into **14** utilizing the Mitsunobu reaction,[23] and subsequent protection provided the C_7 silyl ether. After treatment with DDQ, a careful oxidation with buffered Dess−Martin periodinane[19] provided a high yield of the sensitive aldehyde **15**[24] with no evidence for migration of the β,γ-olefin into conjugation or epimerization of the α-stereocenter. Aldehyde **15** was added to an excess of the lithium enolate derived from methyl acetate, and the resulting 2:1 ratio of aldol adducts[25] was immediately oxidized to the β-keto ester **3** using the Dess−Martin reagent (Scheme 4).

Scheme 4



The critical Stille coupling[26] of stannane **2** and the fully functionalized alkenyl bromide **3** were realized only when reactions were attempted with a palladium catalyst associated with very labile ligands in nonpolar solvent. Thus, the atypical conditions of Pd_2dba_3·$CHCl_3$ in CH_2Cl_2 at room temperature[27] provided diene **16** in 81% isolated yield (Scheme 5) along with a small amount (5−8%) of a presumed diastereomer arising from minor enantiomers of epoxides **4** and **7**. Our exploratory studies for making this

Scheme 5



carbon−carbon bond involved a coupling reaction between stannane **2** and bromide **11**, which also showed that "ligandless" palladium conditions ($Pd(OAc)_2$/toluene) provided the expected diene at room temperature, whereas the addition of triphenylphosphine or various other phosphines and polar solvents (DMF, THF, NMP) afforded none of the product. Furthermore, it is surprising that the use of triphenylarsine in these reactions resulted in none of the desired cross-coupled product even after prolonged reaction times or elevated temperatures.[28]

Intramolecular transesterification was carried out by heating the β-keto ester alcohol (**16**) at reflux in toluene,[29] which gave the pure macrocycle (**17**) in 72% yield presumably via a ketene intermediate.[30] Finally, removal of the silyl ether protecting group gave spontaneous ring closure to a single hemiketal isomer, which proved to be synthetic (−)-amphidinolide P (**1**), isolated as a white crystalline powder: $[\alpha]^{23}_D$ −30° (*c* 0.09, MeOH), $[\alpha]^{25}_D$ lit. +31° (*c* 0.098, MeOH), identical in all respects, except rotation, with detailed spectroscopic data reported for the natural product.[9]

In summary, we have described the first synthetic route to amphidinolide P (**1**), which establishes the absolute configuration of the natural product as opposite to that as depicted and developed for our synthetic material. Furthermore, we have demonstrated mild "ligandless" conditions for a Stille coupling reaction on a highly functionalized

(22) The absolute stereochemistry of **14** was determined by Mosher ester analysis. See: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(23) Mitsunobu, O. *Synthesis* **1981**, 1.

(24) See ref 21b for an example in which the Dess−Martin periodinane was used for a similar oxidation.

(25) Sato, F.; Kusakabe, M.; Kato, T.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1331−1332.

(26) For reviews on the Stille reaction, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 50. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (c) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771−1780. (d) Mitchell, T. N. *Synthesis* **1992**, 803−815.

(27) (a) This catalyst system was previously used for Stille coupling reactions of triflates by Baker, S. R.; Roth, G. P.; Sapino. C. *Synth. Comm.* **1990**, *20*, 2185−2189. (b) For "ligandless" use of Palladium in various couplings, see: Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551.

(28) We were able to couple tributylvinylstannane and bromide **3** using Pd_2dba_3 and Ph_3As in THF, but these conditions did not give any of the desired product for the coupling of **2** and **3** even under prolonged reaction times. For an example of a similar Stille coupling using a vinyl bromide, see: Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237−12254.

(29) (a) Mottet, C.; Hamelin, O.; Garavel, G.; Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380−1382. (b) Bader, A. R.; Cummings, L. O.; Vogel, H. A. *J. Am. Chem. Soc.* **1951**, *73*, 4195−4197. (c) Bader, A. R.; Vogel, H. A. *J. Am. Chem. Soc.* **1952**, *74*, 3992−3994.

(30) (a) Cambell, D. S.; Lawrie, C. W. *J. Chem. Soc., Chem. Commun.* **1971**, 355. (b) Witzeman, J. S. *Tetrahedrom Lett.* **1990**, *31*, 1401.

substrate, which could have important ramifications for the synthesis of complex natural products.

Acknowledgment. The authors gratefully acknowledge the National Institutes of Health (GM-42897) for generous support of our work.

Supporting Information Available: Procedures and spectral data for all compounds on the synthesis pathway and a proton NMR spectrum of **1** (PDF). This material is available via the Internet at http://pubs.acs.org.

OL0000197