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Synthetic Studies toward Amphidinolide B_1: Synthesis of the C_9–C_{26} Fragment

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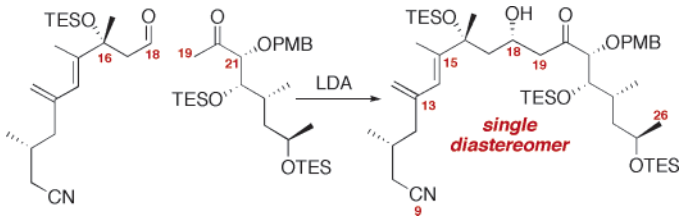
ABSTRACT

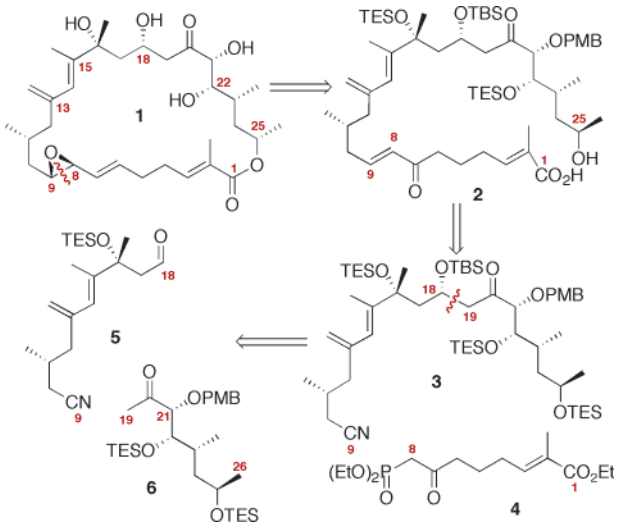


The synthesis of the C_9–C_{26} portion of amphidinolide B_1 is described. A Fleming allylation followed by elimination was employed for the construction of the C_{13}–C_{15} diene portion. Sharpless asymmetric dihydroxylation was utilized for regioselective functionalization of a styrene-derived alkene, in the presence of the C_{13}–C_{15} diene functionality. A highly diastereoselective aldol reaction was developed to establish the C_{18} stereochemistry.

Amphidinolide B_1 (**1**) was first observed in the dinoflagellate *Amphidinium* sp., isolated from the Okinawan flatworm *Amphiscolops* sp. (Scheme 1).[1] The relative stereochemistry of **1** was determined by X-ray crystal analysis,[2] and the absolute stereochemistry was established by degradation.[3] Macrolide **1** is a member of a diverse family of natural products[4] that are potent cytotoxic agents with impressive IC_{50} activity in a series of screens: L1210 murine leukemia cell line (0.14 ng/mL), human colon tumor HCT 116 cell line (0.12 μg/mL), and KB cancer cell line (4.2 ng/mL).[1,2,4,5] The biological activity and complex structural architecture of **1** has led to considerable synthetic interest;[6,7] yet, the total synthesis of **1** remains an elusive target.[8]

Our initial retrosynthetic strategy, as outlined in Scheme 1, involves a Mitsunobu macrolactonization of seco acid **2**.

Scheme 1. Retrosynthetic Strategy for Amphidinolide B_1



Compound **2** could, in turn, be available from Wadsworth−Emmons reaction of a C_9 aldehyde with the phosphonate **4**. A diastereoselective aldol reaction between methyl ketone

(1) Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1127−29.

(2) Bauer, I.; Maranda, L.; Shimizu, Y.; Peterson, R. W.; Cornell, L.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 2657−58.

(3) Ishibashi, M.; Ishiyama, H.; Kobayashi, J. *Tetrahedron Lett.* **1994**, *35*, 8241−42.

(4) For a recent review: Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77−93.

(5) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *J. Nat. Prod.* **1989**, *52*, 1036−41.

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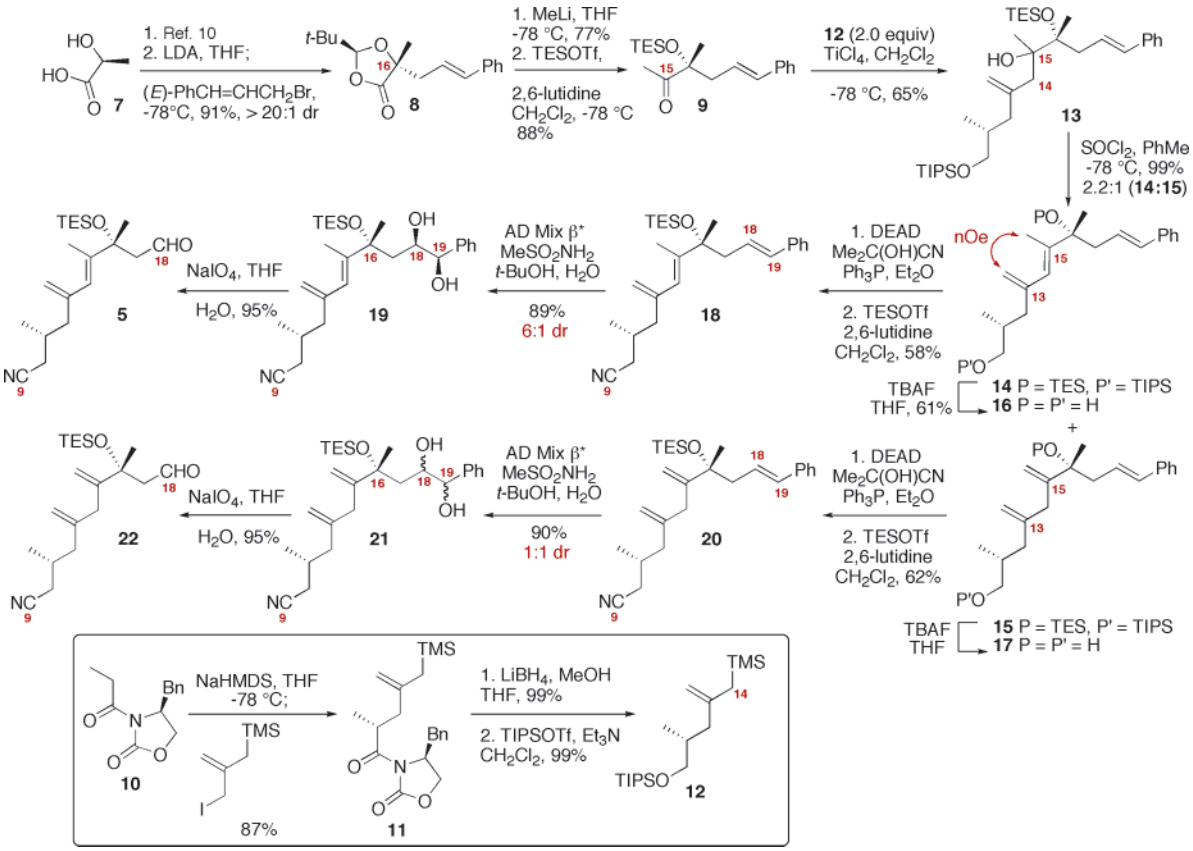
Scheme 2



6 and aldehyde **5** would be used to form the $C_{18,19}$ linkage. Finally, the 1,3-diene fragment present in **5** is particularly challenging as it appears that the C_{16}-alkoxy moiety renders a palladium- or copper-mediated strategy problematic for its formation.[7a,9] For this reason, an alternate method for its construction needed to be developed.

The synthesis of aldehyde **5** began with the commercially available (*S*)-lactic acid (**7**) (Scheme 2). After acetalization with pivaldehyde, Seebach alkylation[10] with cinnamyl bromide provided the tertiary alkoxy function in 91% yield and greater than 20:1 dr. Subsequent treatment with MeLi and silylation yielded the protected methyl ketone **9**. Combination with the readily available allyl silane **12** using freshly distilled $TiCl_4$ yielded the $C_{14,15}$-coupled material **13** in 65−70% yield as 6:1 ratio of diastereomers at C_{15}. Next, elimination of the homoallylic alcohol **13** using $SOCl_2$ and pyridine in toluene provided the $C_{13}-C_{15}$ diene **14** as a *single* stereoisomer at $C_{14}-C_{15}$. The desired product was contaminated with the unconjugated diene **15** in a 2.2:1 ratio (**14**/**15**). While compounds **14** and **15** could be separated by HPLC,

(6) (a) Zhang, W.; Carter, R. G.; Yokochi, A. F. T. *J. Org. Chem.* **2004**, *69*, 2569−72. (b) Carter, R. G.; Zhang, W. 227th ACS National Meeting, Mar 28−Apr 2, 2004, Anaheim, CA; American Chemical Society: Washington, DC, 2004; ORGN-398.

(7) (a) Cid, B.; Pattenden, G. *Tetrahedron Lett.* **2000**, *41*, 7373−78. (b) Lee, D.-H.; Rho, M.-D. *Tetrahedron Lett.* **2000**, *41*, 2573−76. (c) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 571−72. (d) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 573−75. (e) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2275−78. (f) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2279−82. (g) Chakraborty, T. K.; Thippewamy, D. *Synlett* **1999**, 150−52. (h) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1163−66. (i) Chakraborty, T. K.; Thippewamy, D.; Suresh, V. R.; Jayaprakash, S. *Chem. Lett.* **1997**, 563−64. (j) Chakraborty, T. K.; Suresh, V. R. *Chem. Lett.* **1997**, 565−66. (k) Lee, D. H.; Lee, S.-W. *Tetrahedron Lett.* **1997**, *38*, 7909−10. (l) Ohi, K.; Shima, K.; Hamada, K.; Saito, Y.; Yamada, N.; Ohba, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2433−40. (m) Ndubaku, C. O.; Jamison, T. F. 227th ACS National Meeting, Mar 28−Apr 2, 2004, Anaheim, CA; American Chemical Society: Washington, DC, 2004; ORGN-392. (n) Schneekloth, J. S., Jr.; Mandal, A.; Crews, C. M. 228th ACS National Meeting, Aug 22-27, 2004, Philadelphia; American Chemical Society: WAshington, DC, 2004; MEDI-172. (o) Nelson, S. G.; Gopalarathnam, A.; Kassick, A. J. 229th ACS National Meeting, Mar 13-18, 2005, San Diego; American Chemical Society: Washington, DC, 2005; ORGN-413. (p) Mandal, A. K.; Schneekloth, J. S., Jr.; Crews, C. M. *Org. Lett.* **2005**, *7*, 3645−48.

(8) For total syntheses of other members of the amphidinolides: (a) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198−99. (b) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945−48. (c) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765−66. (d) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508−511. (e) Maleczka, R. E.; Terrell, L. R.; Geng, F.; Ward, J. S., III *.Org. Lett.* **2002**, *4*, 2841−44. (f) Trost, B. M.; Chrisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420−21. (g) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374−75. (h) Aïssa, C.; Riveiros, R.; Ragot, J.; Frustner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512−20. (i) Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704−05. (j) Trost, B. M.; Harrington, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 5028−29. (k) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618−19. (l) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970−71. (m) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297−307.

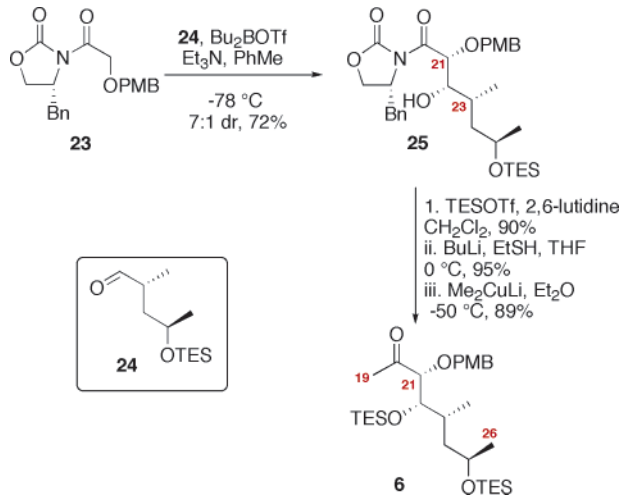
(9) Chakraborty[7g] has shown that the $C_{13}-C_{14}$ palladium coupling can be affected on substrates containing an sp^2-hybridized center at C_{16}. Also, Nelson and co-workers quite recently have disclosed the apparent ability access the $C_{13}-C_{15}$ diene via a Suzuki coupling.[7o]

(10) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−24.

purification of the desilylated compounds **16** and **17** proved logistically easier as they were separable by standard chromatographic methods. Subsequent Mitsunobu-type incorporation of the C_9 cyanide[11] and protection yielded **18**. Next, Sharpless asymmetric dihydroxylation of **18** using AD mix β*[12] provided the $C_{18,19}$ diol as an inconsequential 6:1 mixture of diastereomers. The selectivity for the $C_{18,19}$ alkene over the $C_{13}-C_{15}$ diene was attributed to, in part, a beneficial π-stacking interaction between the neighboring aromatic ring and the corresponding Sharpless ligand.[13] Dihydroxylation under standard OsO_4, NMO conditions provided a complex mixture of products. AD mix α* also proved to be a poor reagent for this transformation. Interestingly, dihydroxylation of the unconjugated diene **20** with AD mix β* was again regioselective for the $C_{18,19}$ alkene; however, no diastereoselectvity was observed in the dihydroxylation. Finally, cleavage of the diol **19** yielded the necessary aldehyde **5**. An analogous procedure with the unconjugated diene series provided the aldehyde **22**.

The synthesis of the eastern subunit **6** commenced with the previously prepared aldehyde **24**[6a] (Scheme 3). Boron-

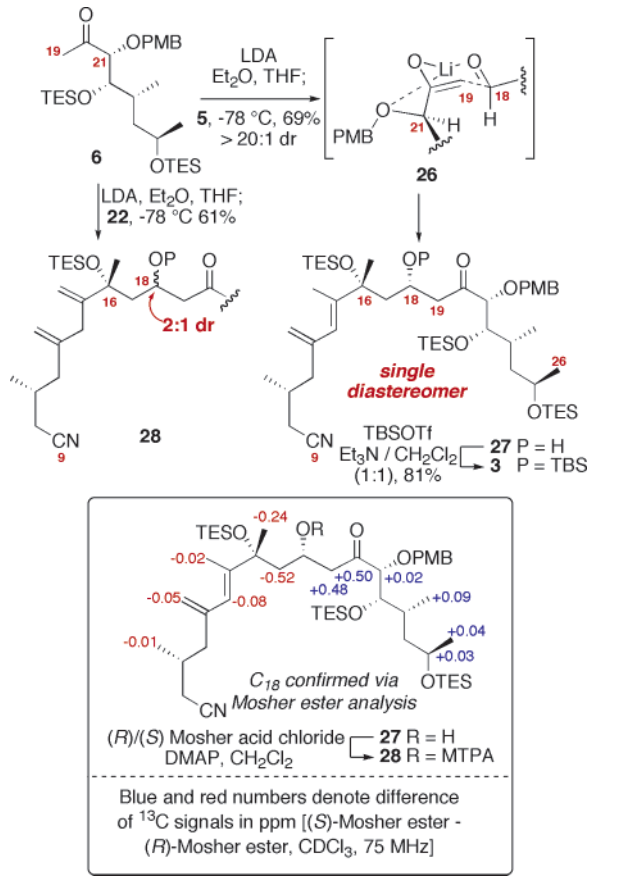
Scheme 3



mediated aldol reaction of aldehyde **24** with the oxazolidinone **23**[14] gave the desired $C_{21}-C_{23}$ *syn*,*syn* adduct **25** in good yield. The minor diastereomer in the aldol appeared to be the *anti* aldol adduct ($J_{H21,H22}$ = 9.0 Hz). Subsequent silylation at C_{22} followed by conversion to the thioester and cuprate addition yielded the desired methyl ketone **6**.

With the methyl ketone subunit **6** and the diene fragment **5** constructed, focus shifted toward their union (Scheme 4).

Scheme 4



Chelation-controlled aldol condensation of lithium enolate derived from the methyl ketone **6** with the aldehyde **5** provided the coupled material **27** in 69% yield as a *single* diastereomer. This result is in contrast to work by Pattenden's and Kobayashi's laboratories in which poor selectivity (approximately 3:2 dr) was observed using enolates derived from LDA, NaHMDS, or KHMDS.[7a,h] In both cases, non-chelating silyl protecting groups[15] were employed on C_{21} of the enolate. We attribute part of the improved selectivity at C_{18} to the use of the α-chelating PMB group on the enolate, as shown in the model **26**. It should be noted, however, that when the analogous aldol reaction with the unconjugated diene-containing aldehyde **22** was preformed, diminished selectivity (approximately 2:1 dr) was observed. The C_{18} stereochemistry of **27** was confirmed by Mosher ester analysis.[16] Finally, silyl protection under specific conditions[17]

(11) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162−69.

(12) AD mix β* = $(DHQD)_2PHAL$ (15.2 mg), $K_2OsO_4 \cdot 2H_2O$ (2.55 mg), K_2CO_3 (293.6 mg), $K_3Fe(CN)_6$ (699.6 mg). Commercially available AD mix β proved to be slow and inefficient.

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(14) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961−63.

(15) (a) Keck, G. A.; Castellino, S. *Tetrahedron. Lett.* **1987**, *28*, 281−84. (b) Frye, S. V.; Eliel, E. *Tetrahedron Lett.* **1986**, *27*, 3223−26. It should be noted that there have been selected examples reported to the contrary: (c) Willard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539−41. (d) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457−60. (e) Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1999**, *40*, 4461−64.

(16) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−96. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−19. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143−47. (d) For a recent review: Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−118.

(17) Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283−306.

[TBSOTf (1.2 equiv), Et_3N/CH_2Cl_2 (1:1)] provided silyl ether **27**. If more traditional silylation conditions were employed [e.g., TBSOTf (1.2 equiv), 2,6-lutidine (1.5 equiv)], migration of the 1,1-disubstituted alkene at C_{13} into the $C_{12}-C_{13}$ trisubstituted position appeared to be observed.

In summary, an efficient approach to the C_9-C_{26} portion of amphidinolide B_1 is disclosed. Key steps in the approach include a novel method for the construction of the $C_{13}-C_{15}$ diene, regioselective dihydroxylation of a styrene derivative using Sharpless AD mix and a highly diastereoselective aldol reaction to form the C_{18} stereocenter. While much has been accomplished toward the total synthesis of **1**, significant challenges remain including the incorporation of the C_6-C_9 epoxy alkene moiety and the nontrivial Mitsunobu macrocyclization of an α,β-unsaturated seco acid.

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Note Added after ASAP Publication. There was an error in Scheme 2 in the version published ASAP August 19, 2005; the corrected version was published September 2, 2005.

Supporting Information Available: Complete experimental procedures are provided, including ^1H and ^{13}C spectra, of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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