Published in final edited form as:

Org Lett. 2005 September 15; 7(19): 4209–4212.

Synthetic Studies toward Amphidinolide B₁: Synthesis of the C₉–C₂₆ Fragment

Wei Zhang and Rich G. Carter

Department of Chemistry, 153 Gilbert Hall, Oregon State University, Corvallis, Oregon 97331

Abstract

The synthesis of the C₉–C₂₆ portion of amphidinolide B₁ is described. A Fleming allylation followed by elimination was employed for the construction of the C₁₃–C₁₅ diene portion. Sharpless asymmetric dihydroxylation was utilized for regioselective functionalization of a styrene-derived alkene, in the presence of the C₁₃–C₁₅ diene functionality. A highly diastereoselective aldol reaction was developed to establish the C₁₈ stereochemistry.

Amphidinolide B₁ (**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 products⁴ that are potent cytotoxic agents with impressive IC₅₀ 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**. Compound **2** could, in turn, be available from Wadsworth–Emmons reaction of a C₉ aldehyde with the phosphonate **4**. A diastereoselective aldol reaction between methyl ketone **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 C₁₆-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.

Correspondence to: Rich G. Carter.

rich.carter@oregonstate.edu.

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 ¹³C spectra, of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The synthesis of aldehyde **5** began with the commercially available (*S*)-lactic acid (**7**) (Scheme 2). After acetalization with pivaldehyde, Seebach alkylation¹⁰ 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 TiCl₄ yielded the C_{14,15}-coupled material **13** in 65–70% yield as 6:1 ratio of diastereomers at C₁₅. Next, elimination of the homoallylic alcohol **13** using SOCl₂ and pyridine in toluene provided the C₁₃–C₁₅ diene **14** as a *single* stereoisomer at C₁₄–C₁₅. 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, 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 C₉ cyanide¹¹ 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 C₁₃–C₁₅ 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 OsO₄, 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 diastereoselectivity 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-mediated aldol reaction of aldehyde **24** with the oxazolidinone **23**¹⁴ gave the desired C₂₁–C₂₃ *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 C₂₂ 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). 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 groups¹⁵ were employed on C₂₁ of the enolate. We attribute part of the improved selectivity at C₁₈ 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 C₁₈ stereochemistry of **27** was confirmed by Mosher ester analysis.¹⁶ Finally, silyl protection under specific conditions¹⁷ [TBSOTf (1.2 equiv), Et₃N/CH₂Cl₂ (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 C₁₃ into the C₁₂–C₁₃ trisubstituted position appeared to be observed.

In summary, an efficient approach to the C₉–C₂₆ portion of amphidinolide B₁ is disclosed. Key steps in the approach include a novel method for the construction of the C₁₃–C₁₅ diene, regioselective dihydroxylation of a styrene derivative using Sharpless AD mix and a highly diastereoselective aldol reaction to form the C₁₈ stereocenter. While much has been accomplished toward the total synthesis of **1**, significant challenges remain including the incorporation of the C₆–C₉ epoxy alkene moiety and the nontrivial Mitsunobu macrocyclization of an α,β -unsaturated seco acid.

Acknowledgment

Financial support was provided by the National Institutes of Health (NIH) (GM63723) and Oregon State University. This publication was also made possible in part by a grant from the NIH – National Institute of Environmental Health Sciences (P30 ES00210). We thank Professor Max Deinzer (Mass Spectrometry Facility, Environmental Health Sciences Center, Oregon State University) and Dr. Jeff Morré (Mass Spectrometry Facility, Environmental Health Sciences Center, Oregon State University) for mass spectral data, Rodger Kohnert (Oregon State University) for NMR assistance, and Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for his helpful discussions.

References

1. Ishibashi M, Ohizumi Y, Hamashima M, Nakamura H, Hirata Y, Sasaki T, Kobayashi JJ. *Chem. Soc., Chem. Commun* 1987;1127–29.
2. Bauer I, Maranda L, Shimizu Y, Peterson RW, Cornell L, Steiner JR, Clardy JJ. *Am. Chem. Soc* 1994;116:2657–58.
3. Ishibashi M, Ishiyama H, Kobayashi J. *Tetrahedron Lett* 1994;35:8241–42.
4. Kobayashi J, Tsuda M. *Nat. Prod. Rep* 2004;21:77–93. [PubMed: 15039836] For a recent review
5. Kobayashi J, Ishibashi M, Nakamura H, Ohizumi Y, Hirata Y, Sasaki T, Ohta T, Nozoe SJ. *Nat. Prod* 1989;52:1036–41.
6. a Zhang W, Carter RG, Yokochi AFT. *J. Org. Chem* 2004;69:2569–72. [PubMed: 15049660] Carter, RG.; Zhang, W. 227th ACS National Meeting; Anaheim, CA; American Chemical Society: Washington, DC. Mar 28–Apr 2, 2004; 2004. p. 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 HM, Myles DC. *Tetrahedron Lett* 1999;40:2275–78. f Eng HM, Myles DC. *Tetrahedron Lett* 1999;40:2279–82. g Chakraborty TK, Thippewamy D. *Synlett* 1999:150–52. h Ishiyama H, Takemura T, Tsuda M, Kobayashi JJ. *Chem. Soc., Perkin Trans* 1999;1:1163–66. i Chakraborty TK, Thippewamy D, Suresh VR, Jayaprakash S. *Chem. Lett* 1997:563–64. j Chakraborty TK, Suresh VR. *Chem. Lett* 1997:565–66. k Lee DH, 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. Ndubaku, CO.; Jamison, TF. 227th ACS National Meeting; Anaheim, CA; American Chemical Society: Washington, DC. Mar 28–Apr 2, 2004; 2004. p. ORGN-392. Schneekloth, JS., Jr.; Mandal, A.; Crews, CM. 228th ACS National Meeting; Philadelphia; American Chemical Society: Washington, DC. Aug 22–27, 2004; 2004. p. MEDI-172. Nelson, SG.; Gopalarathnam, A.; Kassick, AJ. 229th ACS National Meeting; San Diego; American Chemical Society: Washington, DC. Mar 13–18, 2005; 2005. p. ORGN-413. p Mandal AK, Schneekloth JS Jr. Crews CM. *Org. Lett* 2005;7:3645–48. [PubMed: 16092840]
8. For total syntheses of other members of the amphidinolides a Williams DR, Kissel WS. *J. Am. Chem. Soc* 1998;120:11198–99. b Williams DR, Myers BJ, Mi L. *Org. Lett* 2000;2:945–48. [PubMed: 10768193] c Williams DR, Meyer KG. *J. Am. Chem. Soc* 2001;123:765–66. [PubMed: 11456603] d Lam HW, Pattenden G. *Angew. Chem., Int. Ed* 2002;41:508–511. e Maleczka RE, Terrell LR, Geng F, Ward JS III. *Org. Lett* 2002;4:2841–44. [PubMed: 12182569] f Trost BM, Chrisolm JD, Wroblewski ST, Jung M. *J. Am. Chem. Soc* 2002;124:12420–21. [PubMed: 12381177] g Ghosh AK, Liu CJ. *Am. Chem. Soc* 2003;125:2374–75. h Aïssa C, Riveiros R, Ragot J, Frustner A. *J. Am. Chem. Soc* 2003;125:15512–20. [PubMed: 14664598] i Ghosh AK, Gong G. *J. Am. Chem. Soc* 2004;126:3704–05. [PubMed: 15038710] j Trost BM, Harrington PE. *J. Am. Chem. Soc* 2004;126:5028–29. [PubMed: 15099060] k Trost BM, Papillon JPN. *J. Am. Chem. Soc* 2004;126:13618–19. [PubMed: 15493910] l Lepage O, Kattnig E, Fürstner A. *J. Am. Chem. Soc* 2004;126:15970–71. [PubMed: 15584724] m Colby EA, O'Brien KC, Jamison TF. *J. Am. Chem. Soc* 2005;127:4297–307. [PubMed: 15783211]
9. Chakraborty^{7g} has shown that the C₁₃–C₁₄ palladium coupling can be affected on substrates containing an sp²-hybridized center at C₁₆. Also, Nelson and co-workers quite recently have disclosed the apparent ability access the C₁₃–C₁₅ diene via a Suzuki coupling.^{7o}
10. Seebach D, Naef R, Calderari G. *Tetrahedron* 1984;40:1313–24.
11. Andrus MB, Meredith EL, Hicken EJ, Simmons BL, Glancey RR, Ma W. *J. Org. Chem* 2003;68:8162–69. [PubMed: 14535799]
12. AD mix β* = (DHQD)₂PHAL (15.2 mg), K₂OsO₄·2H₂O (2.55 mg), K₂CO₃ (293.6 mg), K₃Fe(CN)₆ (699.6 mg). Commercially available AD mix β proved to be slow and inefficient.

13. a Kolb HC, Andersson PG, Sharpless KB. *J. Am. Chem. Soc* 1994;116:1278–91. b Corey EJ, Guzman-Perez A, Noe MC. *J. Am. Chem. Soc* 1995;117:10805–16. c Mander LN, Morris JC. *J. Org. Chem* 1997;62:7497–99. [PubMed: 11671874] d Carter RG, Weldon D. *J. Org. Lett* 2000;2:3913–16.
14. Evans DA, Gage JR, Leighton JL, Kim AS. *J. Org. Chem* 1992;57:1961–63.
15. a Keck GA, Castellino S. *Tetrahedron. Lett* 1987;28:281–84. b Frye SV, Eliel E. *Tetrahedron Lett* 1986;27:3223–26. It should be noted that there have been selected examples reported to the contrary: c Willard PG, Hintze MJ. *J. Am. Chem. Soc* 1987;109:5539–41. d Evans DA, Allison BD, Yang MG. *Tetrahedron Lett* 1999;40:4457–60. e Evans DA, Halstead DP, Allison BD. *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 JA, Mosher HS. *J. Am. Chem. Soc* 1973;95:512–19. c Sullivan GR, Dale JA, Mosher HS. *J. Org. Chem* 1973;38:2143–47. d Seco JM, Quinoa E, Riguera R. *Chem. Rev* 2004;104:17–118. For a recent review
17. Magnus P, Carter R, Davies M, Elliott J, Pitterna T. *Tetrahedron* 1996;52:6283–306.

Scheme 1.
Retrosynthetic Strategy for Amphidinolide B₁

Scheme 3.

Scheme 4.