J|A|C|S
COMMUNICATIONS

Published on Web 01/09/2004

# Synthesis of Amphidinolide T1 via Catalytic, Stereoselective Macrocyclization

Elizabeth A. Colby, Karen C. O'Brien, and Timothy F. Jamison*

*Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139*

Received November 20, 2003; E-mail: tfj@mit.edu

Since the isolation of amphidinolide A by Kobayashi in 1986,[1] the structural complexity, effects upon biological systems, and scarcity of the amphidinolide natural products have stimulated intense research efforts in several disciplines.[2] A significant feature common to all 35 members of this ever-growing family of molecules is a highly oxygenated and stereochemically rich macrocycle, ranging in size from 12 to 29 atoms. A small fraction of these otherwise diverse natural products have been prepared by total synthesis.[3]

Herein we describe a stereoselective synthesis of amphidinolide T1[4] (Figure 1, **1**), whereby an intramolecular, transition metal-catalyzed reductive alkyne−aldehyde coupling related to methods developed in our laboratories[5,6] and in the Montgomery group[7] assembles the 19-membered macrocycle by formation of the C12−C13 carbon−carbon bond (red ★). In contrast to all previous amphidinolide syntheses,[3] the macrocyclization also addresses a stereochemical issue in the same operation, in this case installation of the C13 stereogenic center (with very high stereocontrol).

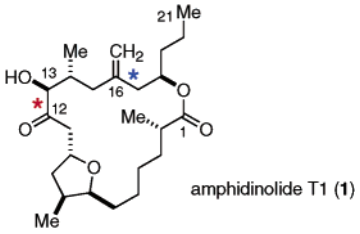


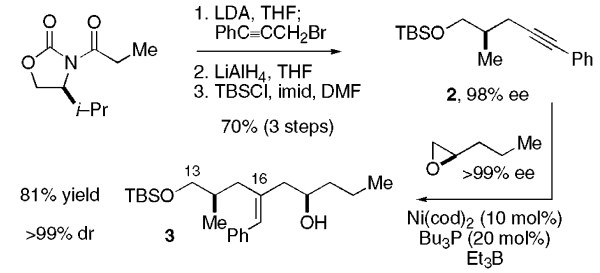

***Figure 1.*** Amphidinolide T1 (**1**). Asterisks indicate carbon−carbon bonds formed using a nickel-catalyzed reductive alkyne−aldehyde (red ★, intramolecular) or alkyne−epoxide (blue ★, intermolecular) coupling.

The catalytic, stereoselective macrocyclization strategy we employed also enabled preparation of the entire C13−C21 fragment (**3**) of the target in only four steps, one of which was another nickel-catalyzed reductive coupling reaction developed in our group: that of an alkyne and an epoxide (Figure 1 (blue ★) and Scheme 1).[8] The construction of nearly half of amphidinolide T1 was thus reduced to the synthesis of two enantiomerically pure coupling partners: an epoxide and an alkyne.

Jacobsen's (salen)Co(III)-catalyzed hydrolytic kinetic resolution efficiently solved the first of these problems, affording *(R)-n*-propyloxirane in >99% ee (Scheme 1).[9] An Evans oxazolidinone auxiliary was used to prepare the requisite alkyne (**2**), by way of a diastereoselective propargylation with 3-bromo-1-phenyl-1-propyne.[10] The Ni-catalyzed, alkyne−epoxide reductive coupling smoothly united these two building blocks, completing the synthesis of this fragment (**3**) of amphidinolide T1 in an average yield of 87% per step and with >95:5 regioselectivity with respect to *both* epoxide ring opening *and* addition to the alkyne.

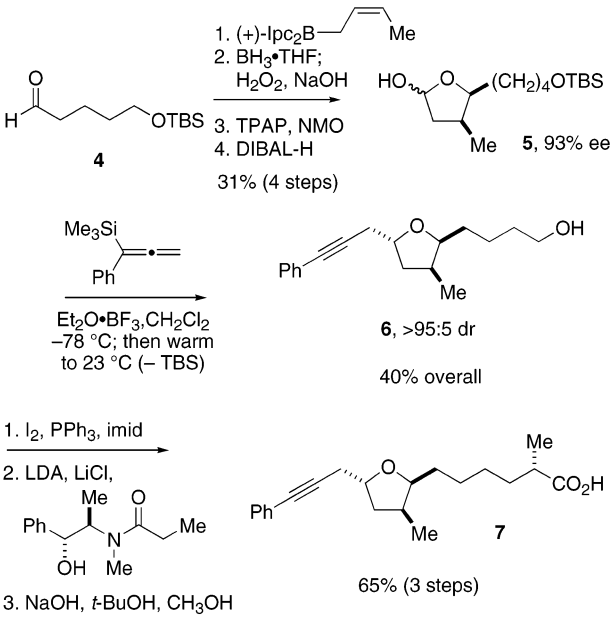
As summarized in Scheme 2, three of the four stereogenic centers in the C1−C12 fragment (**7**) were established in a reagent-controlled fashion, whereas the other capitalized on a strong stereochemical bias[11] in an addition reaction to an oxocarbenium species derived from a lactol (**5**).[12]

***Scheme 1.*** Enantioselective Synthesis of the C13−C21 (**3**) Fragment of **1** Using a Nickel-Catalyzed Alkyne−Epoxide Reductive Coupling




An enantioselective Brown *(Z)*-crotyl addition to aldehyde **4**[13] (93% ee) established the C7−C8 syn relationship,[14] and straightforward functional group manipulation provided **5**.[11] Stereoselective installation of the PhC≡$CCH_2$ group was best accomplished by Lewis acid-promoted allenylsilane addition to hemiacetal **5**, in analogy to Danheiser's method for allenyl addition to aldehydes and acyclic acetals.[15] Warming to ambient temperature effected concomitant removal of the TBS protective group, giving **6** in 40% overall yield and high diastereoselectivity, mirroring the levels of stereoselection observed by Woerpel in a recent series of investigations.[11,12] Because the remaining stereogenic center in this fragment lay remote to those of the tetrahydrofuran, a diastereoselective alkylation using the pseudoephedrine-based chiral auxiliary developed by Myers proved to be the best course of action.[16] In this way, the fully elaborated C1−C12 fragment, carboxylic acid **7**, was afforded in 65% overall yield from **6** (>95:5 dr).

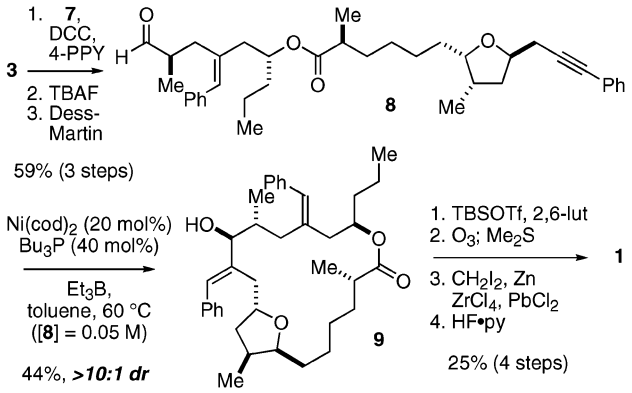
***Scheme 2.*** Synthesis of the C1−C12 Fragment (**7**) of Amphidinolide T1






10.1021/ja039716v CCC: $27.50 

***Scheme 3.*** Synthesis of Amphidinolide T1 (**1**) via Stereoselective Macrocyclization: Intramolecular, Nickel-Catalyzed Alkyne−Aldehyde Reductive Coupling




Fragment coupling via ester formation between alcohol **3** and carboxylic acid **7** and conversion of C13 to an aldehyde set the stage for a nickel-catalyzed reductive macrocyclization of (1,19)-alkynal **8**. To our delight, allylic alcohol **9** was obtained with complete selectivity for the desired configuration of the C13 carbinol,[17] thus completing both assembly of the 19-membered ring and installation of all of the stereogenic centers of amphidinolide T1 (Scheme 3).

Two other features of this stereoselective macrocyclization are noteworthy and compensate for the moderate yield. That the undesired C13 diastereomer was undetectable was surprising because *inter*molecular couplings of closely related compounds were nearly nonstereoselective (1.5:1). Further, even if the intermolecular coupling were perfectly selective, the catalytic macrocyclization led to a significantly shorter synthesis because it obviated protection (and subsequent unmasking) of carboxylic acid **7** and the free hydroxyl group in **3**.

With the macrocycle in hand, the only remaining task was conversion of the C12 and C16 benzylidene groups to a ketone and methylidene, respectively. After investigation of several end-game strategies, we found that protection of the C13 hydroxyl, global ozonolysis, selective methylenation at C16 using a modification of Takai's method,[18] and finally HF−pyridine removal of the TBS protective group afforded amphidinolide T1 (**1**), whose spectroscopic and spectrometric data were identical in every respect to those reported by Kobayashi for the naturally occurring enantiomer.[4]

In conclusion, two nickel-catalyzed, carbon−carbon bond-forming reactions were instrumental in an enantioselective synthesis of amphidinolide T1 (**1**). A catalytic alkyne−epoxide reductive coupling (intermolecular) completed the preparation of one half of **1**, and a catalytic alkyne−aldehyde reductive coupling (intramolecular) simultaneously assembled the macrocycle *and* established the configuration of a stereogenic center with complete selectivity in the desired fashion. This is the most direct synthesis of an amphidinolide T natural product to date, in terms of both longest linear sequence (16 steps from **4**) and total number of synthetic operations (20).[3d,g,h] We are currently developing an analogous, modular strategy for the synthesis of the other amphidinolide T natural products.[4b,c]

**Acknowledgment.** We thank Anna K. Hirsch (Cambridge University-MIT Exchange Program) for experimental assistance. E.A.C. and K.C.O., respectively, thank the American Society for Engineering Education (NDSEG Fellowship) and the Thomas A. Spencer Endowed UROP Fund (MIT). We also thank the National Institute of General Medical Sciences (GM-063755), NSF (CAREER CHE-0134704), Merck Research Laboratories, Johnson & Johnson, Boehringer Ingelheim, Amgen, Pfizer, and GlaxoSmithKline for generous financial support. The NSF (CHE-9809061 and DBI-9729592) and NIH (1S10RR13886-01) provided partial support for the MIT Department of Chemistry Instrumentation Facility.

**Supporting Information Available:** Experimental procedures and data and $^1$H NMR spectra of **1**, **3**, and **6**−**9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5755−5758.

(2) (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753−1769. (b) Kobayashi, J. In *Comprehensive Natural Products Chemistry;* Mori, K., Ed.; New York: Elsevier, 1999; Vol. 8, pp 619−634. (c) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337−342.

(3) Macrolactonization: (a) Amphidinolide J: Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198−11199. (b) P: Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945−948. (c) K: Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765−766. (d) T1: Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374−2375. (e) A (proposed), Stille coupling: Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508−511. Ring-closing metathesis: (f) A (proposed): Maleczka, R. E.; Terrell, L. R.; Geng, F.; Ward, J. S., III. *Org. Lett.* **2002**, *4*, 2841−2844. (g) T4: Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4763−4766. (h) T1: Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512−15520. (i) A (proposed), Ru-catalyzed alkene−alkyne coupling: Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420−12421.

(4) (a) Tsuda, M.; Endo, T.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 1349−1352. (b) Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134−142. (c) Kubota, T.; Endo, T.; Tsuda, M.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2001**, *57*, 6175−6179.

(5) (a) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443. (b) Chan, J.; Huang, W.-S.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221−4223.

(6) (a) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156−166. (b) Synthesis of (−)-terpestacin via intermolecular alkyne−aldehyde reductive coupling based on ref 6a: Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514−11515.

(7) Ni-catalyzed alkynal cyclizations (five- and six-membered rings): (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065−9066. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098−6099. (c) Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106−2107.

(8) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076−8077.

(9) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(10) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. (b) Alkylation using 1-bromo-2-butyne: Savignac, M.; Durand, J.-O.; Genêt, J.-P. *Tetrahedron: Asymmetry* **1994**, *5*, 717−722.

(11) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.

(12) Schmitt, A.; Reissig, H.-U. *Synlett* **1990**, 40−42.

(13) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236−1245.

(14) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919−5923.

(15) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925−3927.

(16) Myers, A. G.; Yang, B. Y.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(17) Assignment based on Mosher ester analysis of **9** and conversion to **1**.

(18) (a) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670. (b) Zirconium alkylidene reagents: Hartner, F. W.; Schwartz, J.; Clift, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 640−641.

JA039716V