J|A|C|S
COMMUNICATIONS

Published on Web 11/30/2006

Total Synthesis of Amphidinolide E

Porino Va and William R. Roush*

Departments of Chemistry and Biochemistry, Scripps Florida, Jupiter, Florida 33458[†]

Received September 14, 2006; E-mail: roush@scripps.edu

The amphidinolides are a family of over thirty biologically active macrolides isolated from a cultured symbiotic dinoflagellate *Amphidinium* species.[1] Many of the amphidinolides exhibit potent antitumor activity against murine lymphoma L1210 and human carcinoma KB cells.[1] In addition, despite being isolated from a common dinoflagellate, the amphidinolides possess a high degree of structural diversity representing many very different molecular scaffolds. As a result of their complex structures, potent biological properties, and low availability from natural sources, the amphidinolides have attracted considerable attention as targets for synthesis and biological evaluation.[2]

As part of a program directed toward the synthesis of tetrahydrofuran-containing natural products,[3] we have developed and report herein a convergent, highly stereocontrolled total synthesis of amphidinolide E (**1**).[4,5]

We envisaged that amphidinolide E could be accessed by elaboration of tetrahydrofuran **2**, which in turn would be synthesized via a [3+2] annulation reaction[6−8] of aldehyde **3** and allylsilane **4** (Figure 1). We anticipated that the *cis*-THF diastereomer **2** would predominate on the basis of our prior studies of this reaction.[8]

The synthesis of **1** commenced with the Swern oxidation of alcohol **5**,[9] which is available in five steps from commercially available isopropylidene dimethyl D-tartrate (Scheme 1). Treatment of the resulting aldehyde with vinyl magnesium bromide followed by a Johnson orthoester Claisen rearrangement[10] of the mixture of diastereomeric allylic alcohols afforded methyl ester **6** in 60% overall yield. Reduction of **6** with DIBAL (−78 °C) yielded the targeted aldehyde **3**.

Allylsilane **4** was synthesized starting from homoallylic alcohol **7**,[11] which is available in high diastereoselectivity from the asymmetric crotylboration[12] of L-glyceraldehyde pentylidene ketal[13] (Scheme 2). Protection of **7** as the *p*-methoxybenzyl ether followed by hydroboration−oxidation of the vinyl group provided primary alcohol **8** (90% yield). Parik−Doering[14] oxidation of **8** and subsequent Corey−Fuchs[15] homologation of the aldehyde furnished alkyne **9** (88%). Acidic hydrolysis of the pentylidene ketal protecting group and oxidative cleavage of the resulting diol afforded aldehyde **10**. Silylallylboration of **10** was accomplished with 9:1 selectivity (90% yield) by using (*E*)-γ-silylallylboronate (*S,S*)-**11**.[16] Protection of the β-hydroxy allylsilane **12** as the triethylsilyl ether provided allylsilane coupling partner **4**.

Treatment of aldehyde **3** and 2.5 equiv of allylsilane **4** with 1 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C provided the *cis*-tetrahydrofuran **2** with >20:1 ds. Excess allylsilane **4** can be recovered in excellent yield (the combined amounts of **2** and recovered **4** accounts for 92% of **4** used). The modest yield of **2** is due to the propensity of **3** to cyclotrimerize under the reaction conditions. The slow-syringe pump addition of **3** into a −78 °C solution of allylsilane **4** and $BF_3{\cdot}Et_2O$ failed to improve the yield. Furthermore, conducting the reaction at temperatures higher than −78 °C resulted in significant Peterson elimination of **4**.

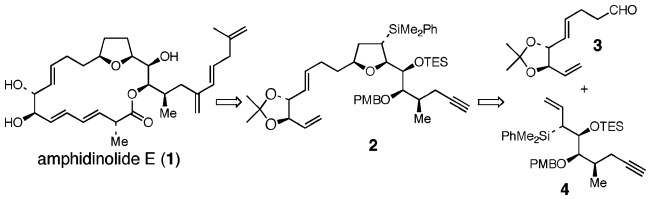
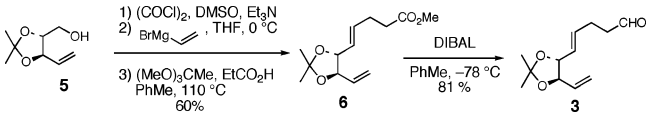
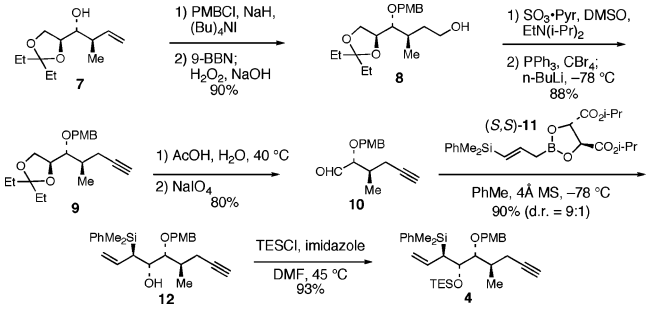


Figure 1. Retrosynthetic analysis of amphidinolide E (**1**).

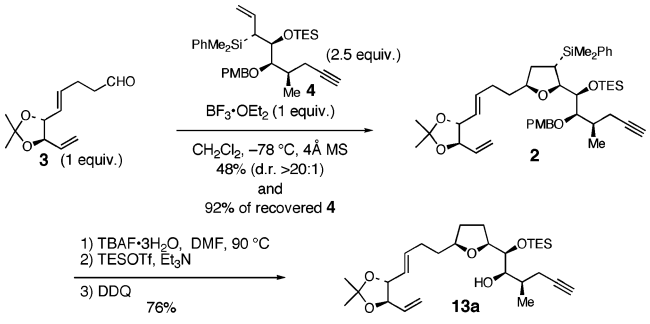
Scheme 1. Synthesis of Aldehyde **3**



Scheme 2. Synthesis of Allysilane **4**



Scheme 3. [3+2] Annulation Reaction of **3** and **4**



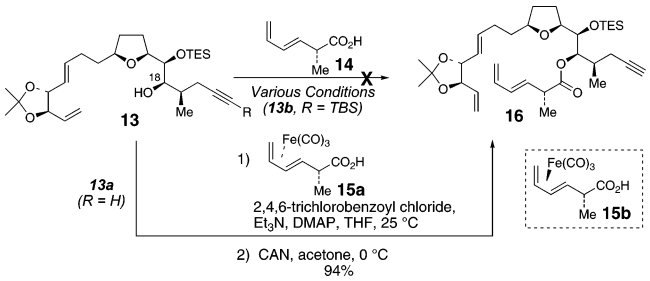
Treatment of [3+2] adduct **2** with solid $TBAF{\cdot}3H_2O$ in DMF at 90 °C effected smooth sp^3 C−Si bond scission with concomitant removal of the triethylsilyl ether (Scheme 3).[17] Reintroduction of the TES ether and subsequent oxidative removal of the *p*-methoxybenzyl group gave alcohol **13a**.

Esterification of the C18 hydroxyl group of **13b** and related intermediates with dienoic acid **14** proved to be astonishingly challenging (Scheme 4). Use of excess amounts (10−20 equiv) of **14** and various coupling reagents invariably failed (see Supporting Information). Whereas in most cases the alcohol was recovered unscathed, the acid component was recovered as the fully conjugated, diene migrated species. No more than trace quantities of **16** could be isolated from these experiments. To remedy this problem,

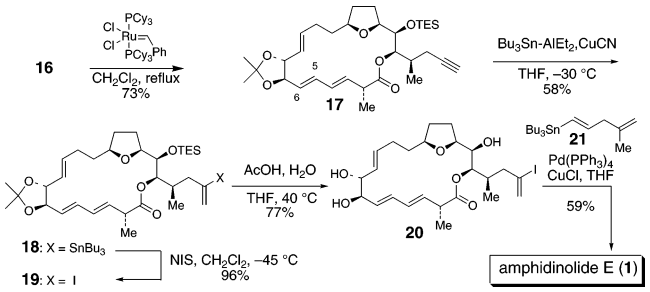
[†] This work was initiated at the University of Michigan, Ann Arbor, MI, 48109.

10.1021/ja066663j CCC: $33.50

Scheme 4. Esterification of Alcohol **13**



Scheme 5. Completion of Amphidinolide E Total Synthesis



we reasoned that use of a "diene protected" analog of acid **14** might be effective. Gratifyingly, esterification of alcohol **13a** using $(CO)_3$Fe-complexed dienoic acid **15a**[18] (1.6 equiv) provided the targeted ester via the modified Yamaguchi method.[19] Oxidative decomplexation of the $(CO)_3$Fe-unit then provided polyene **16** in 94% yield for the two steps. Interestingly, use of the diastereomeric $(CO)_3$Fe-protected dienoic acid **15b** in the esterification−decomplexation sequence did not provide **16**.[20]

Formation of the C5−C6 olefin and closure of the 19-membered macrocycle was achieved by treating **16** with 20 mol % of Grubbs' first generation olefin metathesis catalyst (Scheme 5). The (*E*,*E*)-diene **17** was isolated in 73% yield. In addition, an inseparable mixture of eneyne metathesis products was isolated in 10% yield. Use of the more active Grubbs' second generation or Grubbs−Hoveyda catalysts only resulted in decompostition of polyene **16**. Stannylalumination-protonolysis[21] of the alkyne unit of **17** gave vinylstannane **18** (58%) which was transformed into vinyl iodide **19** by treatment with NIS (96% yield). Acidic hydrolysis of both the triethylsilyl and acetonide protecting groups afforded triol **20** (77% yield). Stille[22] cross coupling of **20** with vinylstannane **21**[5] under the Corey[23] conditions completed the synthesis of (−)-amphidinolide E (59% yield). The spectroscopic properties of synthetic (−)-**1** were in excellent agreement with the literature data reported by Kobayashi and co-workers. Because optical rotation data for natural **1** were unavailable, we repeated the tris-Mosher ester analysis of (−)-**1** as described by Kobayashi.[4b] Our ^{1}H NMR data were in perfect agreement with published NMR data for the tris-Mosher ester derivatives of **1**,[4b] thereby confirming that synthetic (−)-**1** is in fact the naturally occurring enantiomer of amphidinolide E.

In summary, a convergent and highly stereocontrolled synthesis of amphidinolide E has been accomplished. Key steps of this synthesis include a highly diastereoselective $BF_3{\cdot}Et_2O$ promoted [3+2] annulation reaction between aldehyde **3** and allylsilane **4** and a ring closing metathesis reaction of polyene **16**. In addition, we have shown that the $-Fe(CO)_3$ protecting group in **15** is vital to the successful esterification of the hindered hydroxyl group of **13**.

Acknowledgment. This work is supported by the National Institutes of Health (Grants GM38907 and GM38436). We thank Dr. Troy Ryba for assistance with HPLC purification of amphidinolide E and Prof. Jun-ichi Kobayashi for providing comparative spectroscopic data for the natural product.

Note Added after ASAP Publication. After this paper was published ASAP on November 30, 2006, Scheme 4 was revised to show the correct stereochemistry of **15a,b**. The Supporting Information has also been updated with corrected structures. The corrected version was published ASAP on December 6, 2006.

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

References

(1) For reviews on the amphidinolides: (a) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (b) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337. (c) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131.
(2) References to total syntheses of amphidinolides A, J, K, P, T, W, X, and Y are provided in the Supporting Information.
(3) (a) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (b) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865. (c) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818. (d) Mertz, E.; Tinsley, J. M.; Roush, W. R. *J. Org. Chem.* **2005**, *70*, 8035. (e) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245. (f) Lambert, W. T.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5501.
(4) (a) Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421. (b) Kubota, T.; Tsuda, M.; Kobayashi, J. i. *J. Org. Chem.* **2002**, *67*, 1651.
(5) For prior efforts on the synthesis of amphidinolide E: (a) Gurjar, M. K.; Mohapatra, S.; Phalgune, U. D.; Puranik, V. G.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 7899. (b) Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett.* **2005**, *7*, 5331. (c) Note added in proof: while our manuscript was undergoing review, Kim and coworkers reported a total synthesis of amphidinolide E: Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem. Int. Ed.* **2006**, *45*, DOI: http://dx.doi.org/10.1002/anie.200603363.
(6) For reviews of reactions of allylsilanes: (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (b) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173.
(7) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868. (b) Panek, J. S.; Beresis, R. *J. Org. Chem.* **1993**, *58*, 809. (c) Beresis, R.; Panek, J. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1609. (d) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945. (e) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675. (f) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342. (g) Peng, Z.-H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018.
(8) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461.
(9) Sarabia, F.; Sanchez-Ruiz, A. *J. Org. Chem.* **2005**, *70*, 9514.
(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(11) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502.
(12) (a) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (d) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(13) Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587.
(14) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(15) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(16) (a) Roush, W. R.; Grover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567. (b) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981.
(17) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405.
(18) For synthesis of **15** see the SI and (a) Donaldson, W. A.; Craig, R.; Spanton, S. *Tetrahedron Lett.* **1992**, *33*, 3967. (b) Wasicak, J. T.; Craig, R. A.; Henry, R.; Dasgupta, B.; Li, H.; Donaldson, W. A. *Tetrahedron* **1997**, *53*, 4185.
(19) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.
(20) Details of the divergent behavior of **15a** and **15b** in the esterification of **13** will be published separately: Va, P.; Roush, W. R. Submitted for publication.
(21) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064.
(22) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
(23) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

JA066663J