ORGANIC LETTERS

2005
Vol. 7, No. 23
5331−5333

Synthesis of the C6–C21 Segment of Amphidinolide E

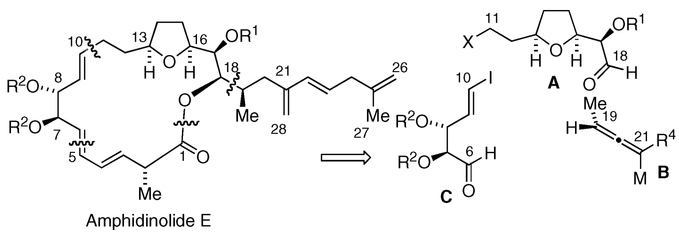
James A. Marshall,* Gregory Schaaf, and Andrew Nolting

Department of Chemistry, University of Virginia, P.O. Box 400319, Charlottesville, Virginia 22904

jam5x@virginia.edu

Received September 28, 2005

ABSTRACT



A convergent approach to a C6–C21 segment of the polyketide amphidinolide E has been developed through combination of three subunits by allenylindium bromide-aldehyde addition and Suzuki sp^2-sp^3 coupling.

The amphidinolides are a family of macrocyclic lactones isolated from the marine dinoflagellates *Amphidinium* sp.[1] Though sharing a common biogenetic ancestry and origin from acetate and propionate, the members of this family display a wide array of structural variation in ring size and carbon skeleton. Structural elements common to many of the members include intraannular tetrahydrofuran, tetrahydropyran, and epoxide rings and the presence of numerous stereo centers. The combination of these diverse structural features and the reported cytotoxicity of the amphidinolides against human tumor cell lines render them attractive targets for total synthesis.[2] In this report we describe some initial efforts directed at amphidinolide E, a member of the family possessing a rare 19-membered lactone ring with an embedded tetrahydrofuran moiety.[3,4]

In our synthetic plan we envisioned a disconnection into four segments, **A**−**D**, which would be joined by Suzuki coupling (**A** and **C**), chiral allenylmetal addition (**A** and **B**), and Wittig condensation (**C** and **D**) (Figure 1). The final ring

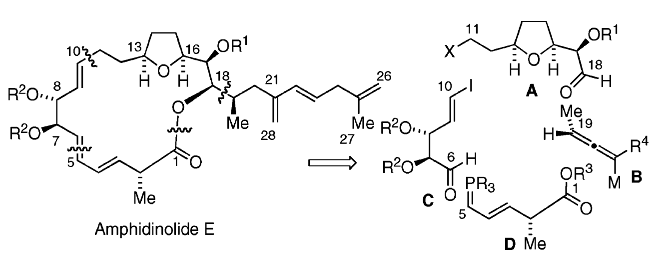


Figure 1. Synthetic plan for amphidinolide E.

closure would be effected by Yamaguchi lactonization. The present report details our successful preparation of segments **A**, **B**, and **C** and their incorporation into a C6−C21 segment of amphidinolide E.

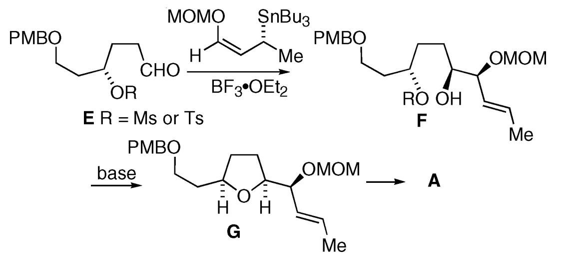
For the synthesis of a tetrahydrofuran precursor of **A** we planned to add a chiral allystannane reagent to aldehyde **E** to prepare a monoprotected *syn*-1,2-diol **F**, which upon base

(1) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543. Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337.
(2) For an overview of synthetic efforts toward the amphidinolide family, see: Aïssi, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512.
(3) Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421. Kubota, T.; Tsuda, M.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 1651.
(4) Synthesis of a C12−C29 segment: Gurjar, M. K.; Mohapatra, S.; Phalgune, U. D.; Puranik, V. G.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 7899.

10.1021/ol0523493 CCC: $30.25
Published on Web 10/15/2005

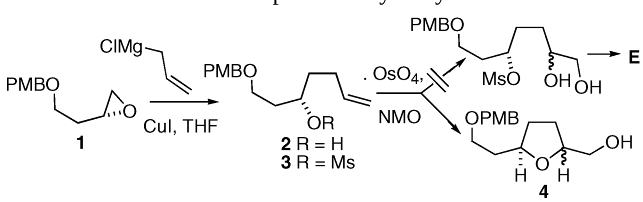
treatment would cyclize to tetrahydrofuran **G** by an internal S_N2 displacement (Scheme 1).[5]

Scheme 1. Proposed Route to Segment **A**



Our initial approach to aldehyde **E** employed the epoxide **1**, prepared by Jacobsen kinetic resolution of the racemate (Scheme 2).[6] Treatment with a Normant allylcuprate reagent[7]

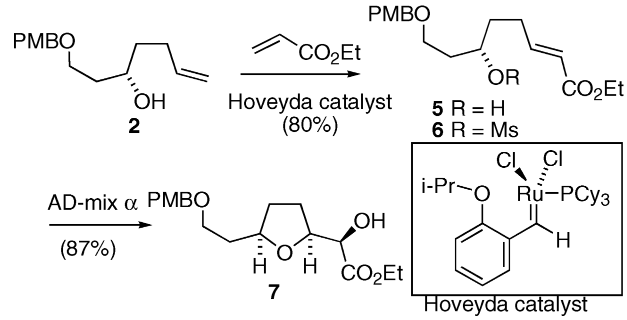
Scheme 2. An Unexpected Dihydroxylation Outcome



afforded the unsaturated alcohol **2**. However, an attempted two-step dihydroxylation-diol cleavage[8] of the unsaturated mesylate **3** failed to produce aldehyde **E** owing to in situ conversion of the presumed diol intermediate to the tetrahydrofuran **4**. Although we could have finessed this unforeseen event through use of a protecting group, the facile cyclization of the diol intermediate suggested an alternative, more direct route to the tetrahydrofuran unit in which a Sharpless asymmetric dihydroxylation would introduce the contiguous oxygenated stereocenters at C16 and C17.[9]

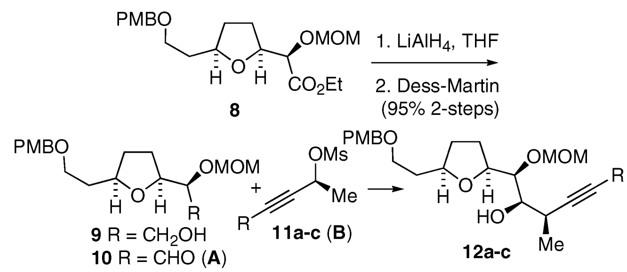
An appropriate dihydroxylation precursor was conveniently prepared by cross-methathesis of alcohol **2** with ethyl acrylate catalyzed by the Hoveyda ruthenium catalyst (Scheme 3).[10] Conversion of the resulting conjugated ester alcohol **5** to the mesylate **6** and dihydroxylation with the Sharpless AD-mix α reagent proceeded as expected with concomitant cyclization to afford the tetrahydrofuran **7** as a >90:10 mixture of separable diastereoisomers in 87% yield.

Scheme 3. Synthesis of Tetrahydrofuran **7**



The hydroxy ester **7** was protected as the MOM ether **8** and subjected to a two-step reduction−oxidation sequence leading to aldehyde **10** (Scheme 4). Several allenylmetal

Scheme 4. Synthesis of Segment **A** and Coupling with **B**



allenylM precursor	conditions	yield, %	anti:syn
11a R = CH_2OAc	$Pd(OAc)_2$•PPh_3 THF, Et_2Zn	18	>95:5
11b R = H	1. Bu_3SnLi, CuBr 2. $InBr_3$, CH_2Cl_2	94[a]	95:5
11c R = TMS	$Pd(OAc)_2$•PPh_3 THF, InI	83	>95:5

[a] Contaminated with tin byproducts.

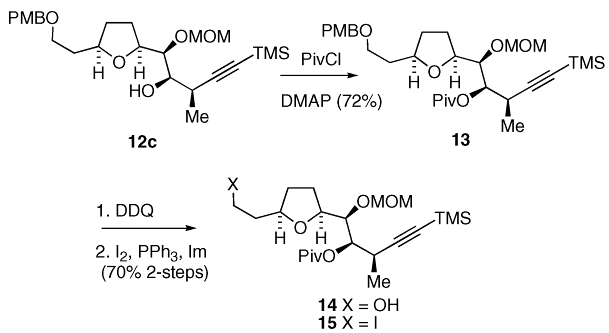
protocols were examined for elaboration of this aldehyde to the various anti adducts **12a**−**c**. In the first of these, the (*S*)-acetoxymethyl-substituted propargylic mesylate **11a**, upon conversion to the (*M*)-allenylzinc reagent and addition to aldehyde **10** in situ, afforded the anti adduct **12a** as the only detectable stereoisomer, but in only 18% yield with recovery of starting material.[11] Extended reaction times failed to increase the yield. Our second effort was more successful. In this approach we employed the (*S*)-mesylate of 3-butyn-2-ol (**11b**) to prepare the (*M*)-allenyltributyl tin reagent, which upon treatment with $InBr_3$ in the presence of aldehyde **13** afforded the adduct **12b** in over 90% yield as a 95:5 mixture of diastereoisomers.[12] Unfortunately, this product was contaminated with tin byproducts that were difficult to separate. Our third and overall preferred route to adduct **12** entailed in situ conversion of the (*S*)-TMS propargylic

(5) Marshall, J. A.; Beaudoin, S.; Lewinski, K. *J. Org. Chem.* **1993**, *58*, 5876.
(6) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360.
(7) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(8) Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1971**, 2583.
(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(10) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(11) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **2002**, *67*, 733.
(12) Marshall, J. A.; Palovich, M. *J. Org. Chem.* **1997**, *62*, 6001.

mesylate **11c** to the (*M*)-allenylindium reagent, which reacted with aldehyde **10** to afford the readily purified adduct **12c** in 83% yield.[13]

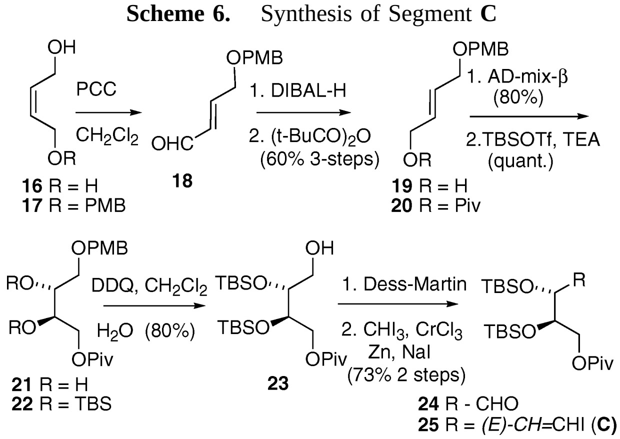
Alcohol **12c** was protected as the pivalic ester **13**, then the PMB group was removed with DDQ in aqueous CH_2Cl_2, and the resulting primary alcohol **14** was converted to the iodide **15** with iodine and Ph_3P in the presence of imidazole (Scheme 5).[14]

Scheme 5. Completion of the **A−B** Segment



Segment **C** of our amphidinolide **A−B−C** array was prepared from the PMB ether derivative **17** of (*Z*)-2-butene-1,4-diol (Scheme 6). Oxidation with PCC proceeded with

Scheme 6. Synthesis of Segment **C**

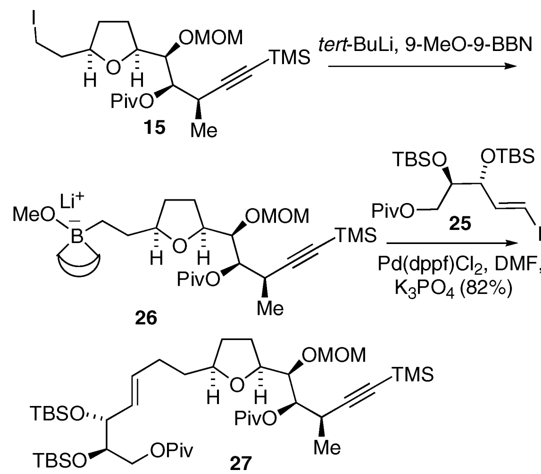


isomerization of the double bond to afford the (*E*)-conjugated aldehyde **18**. This was reduced with DIBAL-H and protected as the pivalic ester **20**. Dihydroxylation with the Sharpless AD-mix β reagent and subsequent silylation of the intermediate diol **21** led to the bis-TBS ether **22**. Cleavage of the PMB ether was effected with DDQ in aqueous CH_2Cl_2 to afford alcohol **23**, which was converted to aldehyde **24** with the Dess−Martin periodinane reagent.[15] Aldehyde **24** was subjected to a Takai condensation with CHI_3, Zn, and catalytic $CrCl_3$ to afford the (*E*)-vinyl iodide **25**, representing fragment **C**, in 73% yield from alcohol **23**.[16]

It is worth noting that prior to the foregoing investigation with the bis-TBS ether **23**, considerable effort was expended on various acetonide analogues with unsatisfactory results owing to the instability of aldehyde intermediates related to **24**. The corresponding TBS ether derivative, on the other hand, proved quite tractable.

For completion of the **A−B−C** fragment synthesis we planned to employ the Suzuki sp^2-sp^3 coupling reaction that had served so well in our previous syntheses of discodermolide, callystatin A, and leptofuranin (Scheme 7).[17] The

Scheme 7. Coupling of Segments **A−B** and **C**



present application proved no exception. In situ conversion of iodide **15** to the boronate **26** with *t*-BuLi and 9-methoxy-9-BBN followed by addition to a mixture of vinyl iodide **25**, K_2CO_3, and $Pd(dppf)Cl_2$ afforded the coupled product **27** in 82% yield.

The foregoing sequence provides a promising approach to the synthesis of tetrahydrofuran-containing polyketides in the amphidinolide family. Future work can now be directed at the nontrivial elaboration and incorporation of segment **D** and the polyene side chain (Figure 1).

Acknowledgment. Support for this work was provided by research grant R01 CA090383 from the National Cancer Institute.

Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0523493

(13) Marshall, J. A.;, Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369.

(14) Corey, E. J.; Pyne, S. H.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883.

(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(16) Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, *8*, 1268.

(17) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014. Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2002**, *67*, 2751. Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428.