Total Synthesis of (+)-Amphidinolide K

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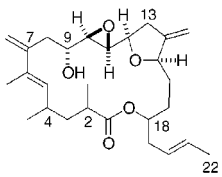
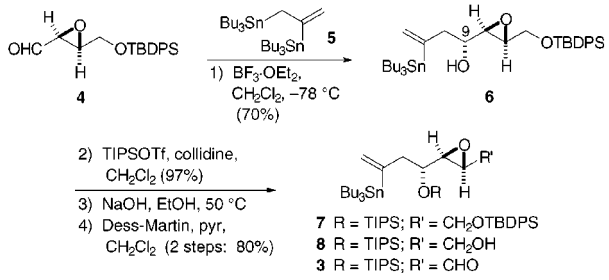
The amphidinolides are an important family of antitumor macrolides isolated from the marine dinoflagellate *Amphidinium* sp., a symbiotic microalgae found in the Okinawan flatworm *Amphiscolops* sp.[1] Amphidinolides have extraordinary activity against a variety of NCI tumor cell lines. However, extremely limited quantities have slowed the pace of biological studies, and in many cases hampered progress toward complete structural assignments.[2] Interestingly, amphidinolides A through V exhibit remarkable structural diversity, ranging from 12-membered to 29-membered systems.[3] Our recent efforts have reported the first total syntheses of amphidinolides J and P,[4] and numerous reports of continuing studies in other laboratories are evidence of widespread interest in these metabolites.[5] In 1993, amphidinolide K was first described as the 19-membered lactone **1** with undetermined stereogenicity at C_2, C_4, and C_{18}.[6] Herein, we report the total synthesis of (+)-amphidinolide K (**2**), and communicate new assignments of relative and absolute stereochemistry of the natural product.



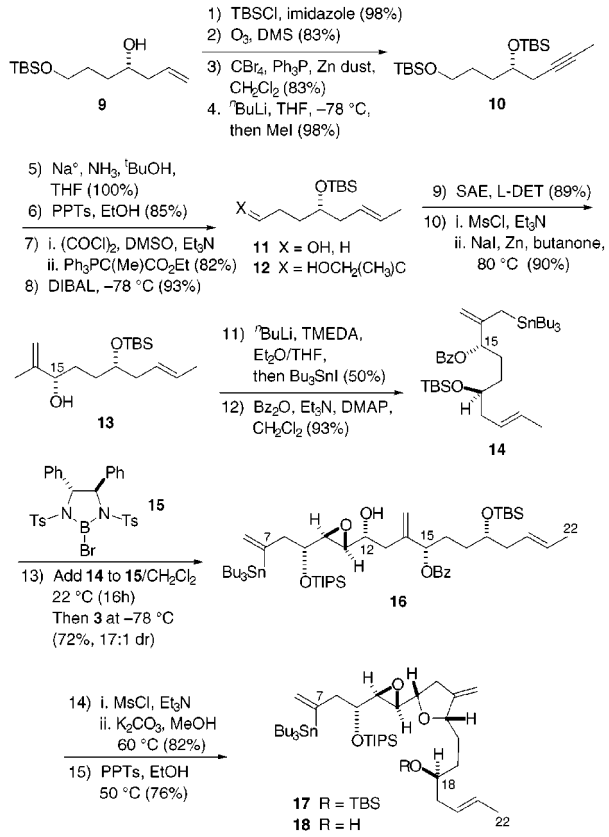
(1) Proposed Structure for Amphidinolide K

A convergent, stereocontrolled synthesis of **1** relied on the efficient preparation of three construction components derived from bond disconnections at (C_6−C_7), (C_{12}−C_{13}), and (C_1−O), which would allow for a flexible plan in light of the challenging stereochemical issues.[7] The first component, optically active aldehyde **3**, was prepared via the readily accessible nonracemic epoxy-aldehyde **4** (Scheme 1). Lewis acid-catalyzed allylation[8] of **4** with bis-stannane **5**[9] gave alcohol **6** as the major diastereomer (79%, 6.9:1 anti:syn), resulting from Felkin-Anh addition. After chromatographic purification of the anti isomer **6**, protection as the triisopropylsilyl (TIPS) ether was followed by selective removal of the primary TBDPS ether under basic conditions. No products resulting from Payne rearrangement of the epoxide were detected throughout the sequence, and mild oxidation[10] of **8** provided aldehyde **3**.

Scheme 1



Scheme 2



Construction of the C_7−C_{22} segment (Scheme 2) was designed to utilize an asymmetric allylation strategy to efficiently fuse stereochemical features in **3** with those of stannane **14**. Known alcohol **9**[11] incorporated C_{18} chirality at an early stage in the synthesis, and the efficient eight-step conversion to allylic alcohol **12** proved uneventful. A Sharpless asymmetric epoxidation of **12** (97% de) and subsequent reductive transposition established

(1) (a) For reviews on isolation of the amphidinolides, see: Kobayashi, J. In *Comprehensive Natural Products Chemistry*; Mori, K., Ed.: Elsevier: New York, 1999; Vol. 8, pp 619−634. (b) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543.

(2) (a) Amphidinolide N displays antitumor potency (IC_{50} = 0.05 nM) similar to levels reported for the spongistatins: Ishibashi, M.; Yamaguchi, N.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1455. (b) Related carbenolide I shows promising in vivo potency: Bauer, I.; Maranda, L.; Young, K. A.; Shimizu, Y.; Fairchild, C.; Cornell, L.; MacBeth, J.; Huang, S. *J. Org. Chem.* **1995**, *60*, 1084. (c) Amphidinolide B: Bauer, I.; Maranda, L.; Shimizu, Y.; Peterson, R. W.; Cornell, L.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 2657.

(3) For recent examples: (a) Kobayashi, J.; Shimbo, K.; Sato, M.; Shiro, M.; Tsuda, M. *Org. Lett.* **2000**, *2*, 2805. (b) Tsuda, M.; Endo, T.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 1349. (c) Tsuda, M.; Endo, T.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 14565.

(4) (a) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198. (b) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.*, **2000**, *2*, 945.

(5) (a) For recent studies directed toward the amphidinolides, see: Williams, D. R.; Meyer, K. G. *Org. Lett.* **1999**, *1*, 1303. (b) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 573. (c) Terrell, L. R.; Ward, J. S., III; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1999**, *40*, 3097. (d) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1163. (e) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2275. (f) Chakraborty, T.; Thippeswamy, D. *Synlett* **1999**, 150. (g) Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 703. (h) Chakraborty, T. K.; Das, S. *Chem. Lett.* **2000**, 80.

(6) Ishibashi, M.; Sato, M.; Kobayashi, J. *J. Org. Chem.* **1993**, *58*, 6928.

(7) We have prepared 25 distinct diastereomers of **1**. Detailed proton NMR studies were supported by MM2* force field calculations (MacroModel 7.0) for conformational analyses of these macrocycles. A detailed discussion of these efforts will accompany a full account of our work.

(8) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Howe, G. P.; Wang, S.; Proctor, G. *Tetrahedron Lett.* **1987**, *28*, 2629.

(9) Mitchell, T. N.; Kwetkat, K.; Rutschow, D.; Schneider, U. *Tetrahedron* **1989**, *45*, 969.

(10) Boeckman, R. K.; Shao, P.; Mullins, J. J. *Org. Synth.* **1999**, *77*, 141.

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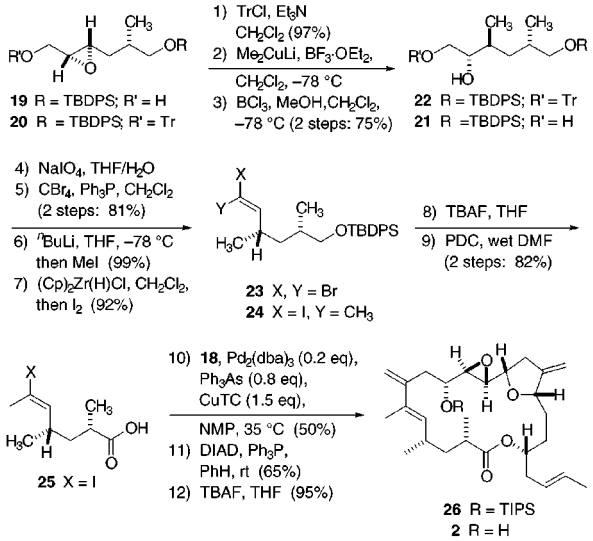
the C_{15} stereochemistry, and provided pure **13** after flash chromatography (80% yield from **12**). Finally, an alkoxide-assisted allylic deprotonation led to stannane **14**.[12]

Formation of (*R*)-homoallylic C_{12} alcohol **16** was achieved by initial transmetalation of optically pure stannane **14** with (*R,R*)-bromoborane **15**[13] via allylic transposition to yield an intermediate borane. Introduction of aldehyde **3** at −78 °C provided for a facile condensation reaction yielding **16** (72%). Stereocontrol is induced from the 1,2-diphenylethane sulfonamide auxiliary and is predicted from a Zimmerman−Traxler model with minimized steric repulsions.[14] The high level of selectivity (17:1 dr) obtained in this case is the result of a matched diastereomeric transition state featuring the inherent Felkin-Anh selectivity for nucleophilic attack in aldehyde **3**, with the (*S*)-configuration of the C_{15} benzoate of **14**, as well as the (*R,R*)-antipode of auxiliary **15**, resulting in 3-fold stereodifferentiation. Conversion of **16** to the corresponding mesylate and methanolysis of the C_{15} benzoate provided for intramolecular backside displacement at C_{12} to give the desired 3-methylene-*cis*-tetrahydrofuran **17** (82%).[15] Finally, desilylation under mild acidic conditions proceeded without significant protodestannylation to yield key intermediate **18**.

Preparation of the C_1-C_6 component required an adaptable route of high stereochemical fidelity to assess elements of stereogenicity at C_2 and C_4. For this purpose, the known oxirane **19**[16] was transformed to the triphenylmethyl (Tr) ether **20**, and regioselective nucleophilic addition of Me_2CuLi in the presence of $BF_3{\cdot}OEt_2$ followed by deprotection gave 1,2-diol **21** as the major isomer (10:1 ratio). Direct reaction of epoxide **20** with $AlMe_3$ gave **22** (20% yield) along with numerous byproducts, whereas cuprate reactions required the sterically demanding protecting unit to minimize competing production of the corresponding 1,3-diol.[4b,17] Subsequent oxidative cleavage of **21** gave an aldehyde that was immediately converted to dibromoolefin **23** in good yield (81%, 2 steps).[18] Elimination and methylation produced a disubstituted alkyne for a regioselective (9:1 ratio) syn hydrozirconation−iodination process affording vinyl iodide **24** (91% over 2 steps). Desilylation and oxidation of the resulting primary alcohol with pyridinium dichromate (PDC) gave the carboxylic acid **25**.

The Stille coupling of alkenylstannane **18** and **25** was a crucial development for our synthesis. Indeed, the formation of butadienes featuring internal (C_2/C_3) dialkyl substitution is particularly challenging.[19,20] Successful coupling of **18** and **25** occurred upon

Scheme 3



mild heating at 35 °C in the presence of palladium(0) catalyst and copper(I) thiophene-2-carboxylate (CuTC)[21] to give the desired seco-acid. Cocatalyst CuTC resulted in a dramatic improvement compared to CuI, and no products were observed in the absence of CuTC. In the absence of palladium(0), only homocoupling of stannane **18** was detected. Macrolactonization with inversion at C_{18} proceeded under Mitsunobu conditions,[22] and deprotection of the C_9 alcohol provided (+)-amphidinolide K (**2**: $[\alpha]_D^{24}$ +62.0° (*c* 0.05, MeOH)), which proved to be the antipode of the natural macrolide.[23] Furthermore, a single-crystal X-ray diffraction study of **2** (mp 114−118 °C) has unambiguously confirmed our stereochemical assignments.[24]

In summary, the execution of a highly convergent strategy has led to completion of the first total synthesis of amphidinolide K. These efforts have led to the establishment of the relative stereochemistry, as well as the absolute configuration of the natural product. Our report of the use of CuTC as a cocatalyst in the Stille reaction is an important development for the preparation of substituted dienes, and holds considerable potential for use in related cross-coupling processes.

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Supporting Information Available: Procedures and spectral data for compounds **2**, **3**, **6**−**8**, **13**−**18**, and **24**−**26** of the synthesis pathway, tables of ^1H and ^{13}C data for **2** and natural amphidinolide K, and data of the X-ray crystal study of **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.
(12) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408.
(13) Corey, E. J.; Yu, G.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5493, 5495.
(14) (a) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P. *Tetrahedron Lett.*, **1998**, *39*, 7251. (b) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924.
(15) For related studies of palladium-induced tetrahydrofuran formation: Williams, D. R.; Meyer, K. G. *Org. Lett.* **1999**, *1*, 1303.
(16) (a) Boeckman, R. K.; Barta, T. E.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091. (b) Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, *56*, 5496.
(17) Tung, R. D.; Rich, D. H. *Tetrahedron Lett.* **1987**, *28*, 1139.
(18) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(19) Formation of similar dienes is unprecedented via the Stille coupling process. For reviews: (a) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235. (b) Mitchell, T. N. *Synthesis* **1992**, 803.
(20) Our studies have shown that vinyl stannanes, such as **18**, have a propensity to undergo *cine* substitution rather than *ipso* replacement. (See: Farina, V.; Hossain, M. A. *Tetrahedron Lett.* **1996**, *37*, 6997.) In addition, iodide **25** was thermally unstable above 60 °C.
(21) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
(22) Li, K. W.; Wu, J.; Xing, W.; Simon, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 7237 and references therein.
(23) We gratefully acknowledge Dr. Jun'ichi Kobayashi, Hokkaido University, Sapporo, Japan, for providing spectral data of authentic material for comparison.
(24) The stereochemical features of synthetic (+)-amphidinolide K (**2**) were confirmed by a single-crystal X-ray diffraction study at −165 °C. Data are available in the Supporting Information.