# Total Synthesis of (+)-Amphidinolide J

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The amphidinolides are a family of important biologically active macrolides isolated from the marine dinoflagellate *Amphidinium* sp., a symbiotic microalga found in the Okinawan flatworm *Amphiscolops* sp.[1] The amphidinolides have shown extraordinary activity against a variety of NCI tumor cell lines. However, the fact that there are extremely limited quantities has slowed the pace of biological studies and, in many cases, hampered progress toward complete structural assignments of these unusual macrolides.[2] Interestingly, this family of metabolites exhibits remarkable structural diversity with twenty-one reported examples of amphidinolides A through S, illustrative of macrocycle formation ranging from twelve-membered to twenty-seven membered systems.[3] Amphidinolide J (**1**) was the first of the
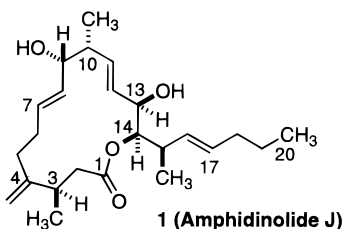

1 (Amphidinolide J)

family in which the relative and absolute stereochemistries were defined.[4] Very recently, isomeric amphidinolide R was discovered as the 14-membered macrolactone formed from esterification of the C-13 hydroxyl of a common seco acid leading to **1**.[5] Herein we report the total synthesis of (+)-amphidinolide J (**1**), and thus communicate the first successful route for total synthesis of a macrolide of the amphidinolide family.

Our convergent, stereocontrolled synthesis of **1** was executed from three subunits which were fashioned from considerations of disconnections of C$_1$−O (lactonization), C$_6$−C$_7$, and C$_{12}$−C$_{13}$ bonding. Current studies in our laboratories have explored recent advances in organozinc chemistry as a significant development for the preparation of these functionalized macrolactones.

As illustrated in Scheme 1, the first component, optically active iodide **2**, was prepared via the conjugate addition of the Yamamoto organocopper species[6,7] derived from the vinyl bromide **3**.[8] Low-temperature addition to the (*S*)-4-phenyl-*N*-enoyloxazolidinone **4**[9] produced the imide **5** ([α]$^{24}_D$ +31.1 (*c* 7.75, CHCl₃)) in 95% yield with complete diastereoselectivity. Asymmetric induction at C-3 (**2**) can be attributed to the exclusive *re*-

Scheme 1
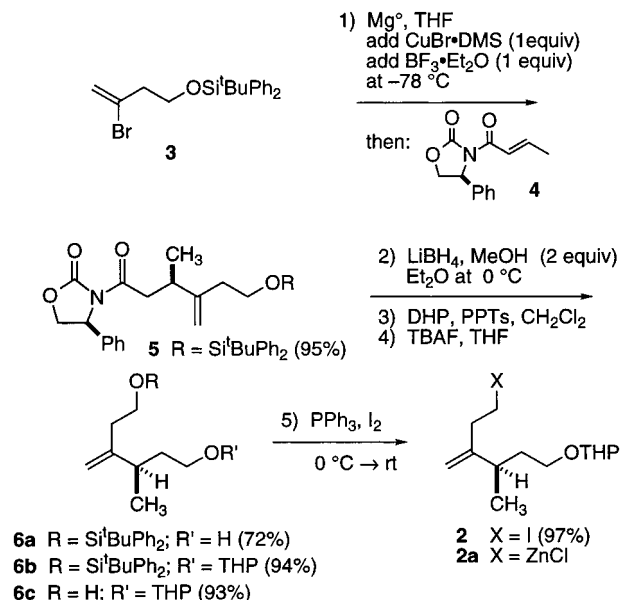
face addition to the bis-chelated *syn*-s-*cis* conformer of **4**. Further conversions to homoallylic iodide **2** proceeded in excellent overall yield.

Coupling reactions for stereocontrolled formation of the *E*-C$_7$−C$_8$ alkene were undertaken using the *E*-vinyl iodide **10** (Scheme 2). The production of **10** utilized the base-induced elimination of the chloro-epoxide **8**, which was accessible from the Sharpless asymmetric epoxidation product **7**.[10] Hydrozirconation of **9** ensured formation of the desired alkene **10** via *syn*-addition.[11] Unfortunately, attempted alkylations of the alkenyllithium or cuprate intermediates derived from **10** promoted facile eliminations of iodide **2** to its corresponding diene. The problem was overcome by formation of the stable homoallylic zinc reagent **2a** (Scheme 1). This novel, well-behaved alkylzinc displayed no products of dimerization, cyclopropylcarbinyl tautomerism, or β-elimination (formation from **2**; ᵗBuLi (2 equiv), THF at −78 °C; then ZnCl₂ (1 equiv), −78 °C → rt).[12,13] Application of the Negishi protocol[12] for palladium-catalyzed reaction of **2a** with **10** was highly successful. In this fashion, palladium coupling of the functionalized homoallylzinc species forged a versatile and stereospecific synthesis of the 1,5-diene **11** (Scheme 2). Utilization of the Takai reaction[15] produced alkene **12a** in 77% yield

(1) (a) Kobayashi, J.; Shigemori, H.; Ishibashi, M.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Org. Chem.* **1991**, *56*, 5221. (b) Kobayashi, J. *J. Nat. Prod.* **1989**, *52*, 225. For a review: Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753.

(2) (a) Ishibashi M.; Sato, M.; Kobayashi, J. *J. Org. Chem.* **1993**, *58*, 6928. (b) Bauer, I.; Maranda, L.; Shimizu, Y. *J. Am. Chem. Soc.* **1994**, *116*, 2657.

(3) Ishibashi, M.; Kobayashi J. *Heterocycles* **1997**, *44*, 543.

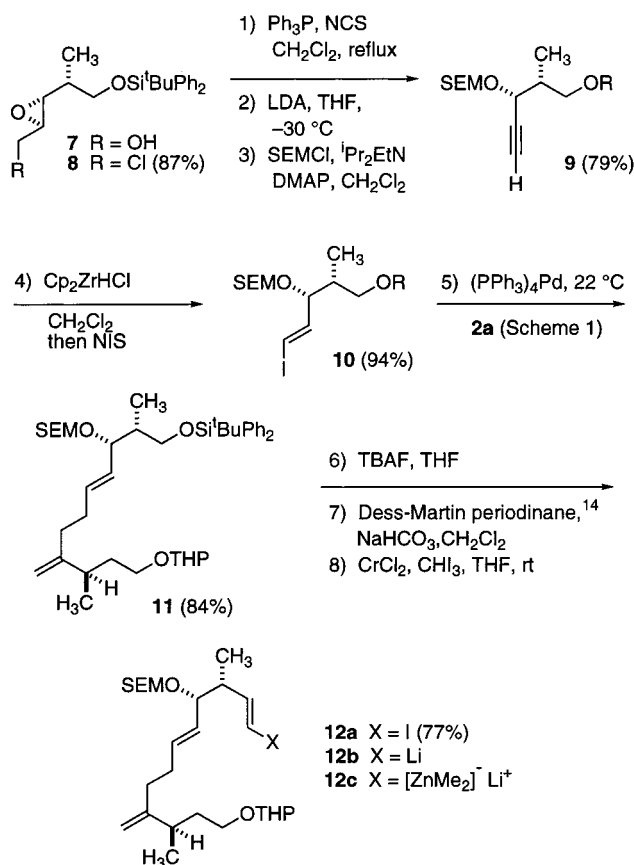(4) Kobayashi, J.; Sato, M.; Ishibashi, M. *J. Org. Chem.* **1993**, *58*, 2645.

(5) Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 7827.

(6) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947.

(7) For recent examples of related asymmetric conjugate additions in natural product synthesis: Williams, D. R.; Li, J. *Tetrahedron Lett.* **1994**, *35*, 5113. Rzasa, R. M.; Shea, H. A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591.

(8) Bromoboration of 4-(*tert*-butyldiphenylsilyloxy)-1-butyne with *B*-bromo-9-borobicyclononane (CH₂Cl₂) followed by HOAc/NaOAc quench provided **3** in 83% yield. Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(9) Nicolás, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766. Hruby, V. J.; Han, Y. *Tetrahedron Lett.* **1997**, *38*, 7317. For a survey of conjugate additions of Yamamoto-based reagents using the 4-phenyl-*N*-enoyloxazolidinone auxiliary: Williams, D. R.; Kissel, W. S.; Li, J. *Tetrahedron Lett.* **1998**, *39*, 8593.

(10) Epoxide **7** was obtained in nearly quantitative yield (de > 95%) as previously reported: Williams, D. R.; Jass, P. A.; Tse, H.-L. A.; Gaston, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4552.

(11) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895. Quenching the intermediate alkenyl zirconium species with iodine caused cleavage of the uncharacteristically labile C-9 SEM ether.

(12) Although functionalized homoallylic zinc derivatives have received little attention in complex molecule synthesis, the advantages of 3-butenylzincs in coupling reactions have been discussed. Negishi, E.; Áy, M.; Gulevich, Y. V.; Noda, Y. *Tetrahedron Lett.* **1993**, *34*, 1437.

(13) A novel methylene insertion offers opportunities for generation of functionalized homoallylic zinc species. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(14) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(15) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. Owing to the presence of α-branching in the precursor aldehydes, high proportions of the *E*-alkenes were obtained without the use of dioxane.

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Scheme 2

1) Ph$_3$P, NCS
CH$_2$Cl$_2$, reflux

2) LDA, THF,
−30 °C

3) SEMCl, ^{i}Pr$_2$EtN
DMAP, CH$_2$Cl$_2$

7 R = OH
8 R = Cl (87%)

9 (79%)

4) Cp$_2$ZrHCl

CH$_2$Cl$_2$
then NIS

10 (94%)

5) (PPh$_3$)$_4$Pd, 22 °C

2a (Scheme 1)

6) TBAF, THF

7) Dess-Martin periodinane,[14]
NaHCO$_3$,CH$_2$Cl$_2$

8) CrCl$_2$, CHI$_3$, THF, rt

11 (84%)

12a X = I (77%)
12b X = Li
12c X = [ZnMe$_2$]$^-$ Li$^+$

for the two-step oxidation-olefination procedure as a 15:1 ratio of *E*/*Z*-isomers with no evidence of epimerization of the C-10 stereocenter.
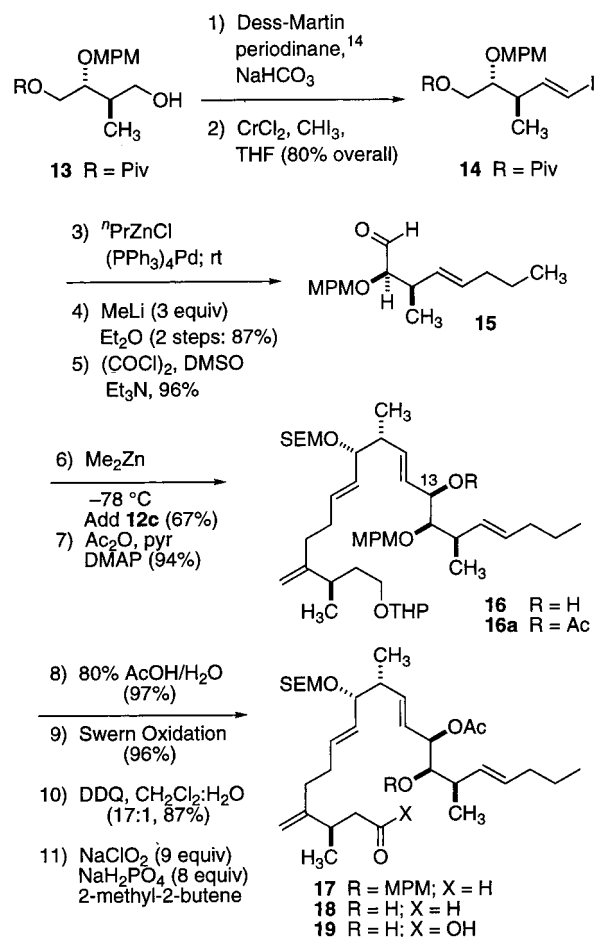
As illustrated in Scheme 3, the optically active 2-methyl-1,3,4-butanetriol derivative **13**[16] served as a precursor to aldehyde **15** for incorporation of the C$_{13}$–C$_{20}$ segment. Oxidation of **13** produced an aldehyde which suffered partial epimerization upon flash chromatography. To avoid this problem, dilution of crude oxidation mixtures with hexanes and filtration afforded product which could be used directly in the subsequent Takai reaction[15] to **14** (*E*/*Z* ratio 19:1). Palladium-catalyzed coupling of **14** with *n*-propylzinc chloride[12] led to desired aldehyde **15**. Studies to join **15** and the alkenyllithium **12b** (Scheme 2: ^{t}BuLi (2.2 equiv), THF at −78 °C) gave poor yields of the diastereomeric C-13 alcohols (1:1 ratio). However, conversion to dimethylalkenyl-zincate **12c** (**12b**; then Me$_2$Zn (1.5 equiv)) provided exclusive formation of **16**. Although the nucleophilic behavior of similar mixed zincates is generally not well characterized,[17] the reaction proceeded with selective transfer of the *E*-alkenyl group,[18] producing the stereochemical result of a chelation-controlled model. Standard operations led to intermediate aldehyde **17**, and the noteworthy DDQ deprotection of **17** to the C-14 hydroxy-aldehyde **18** permitted selective sodium chlorite oxidation to seco-acid **19**.

(16) Alcohol **13** was prepared from 2*R*,3*R*-4-(*tert*-butyldiphenylsilyloxy)-3-methyl-1,2-butanediol with appropriate protecting groups via slight modification of the previously reported four-step pathway; see ref 10. Also: Jass, P. A.; Ph.D. Thesis, Indiana University, 1994.

(17) To our knowledge, this appears to be the first description of a mixed zincate for natural product synthesis. For examples of triorganozincate additions to aldehydes: Kondo, Y.; Takazawa, N.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. I* **1995**, 1207. Kondo, Y.; Takazawa, N.; Yamazaki, C.; Sakamoto, T. *J. Org. Chem.* **1994**, *59*, 4717.

(18) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581.

Scheme 3

1) Dess-Martin
periodinane,[14]
NaHCO$_3$

2) CrCl$_2$, CHI$_3$,
THF (80% overall)

13 R = Piv

14 R = Piv

3) ^{n}PrZnCl
(PPh$_3$)$_4$Pd; rt

4) MeLi (3 equiv)
Et$_2$O (2 steps: 87%)

5) (COCl)$_2$, DMSO
Et$_3$N, 96%

15

6) Me$_2$Zn

−78 °C
Add **12c** (67%)

7) Ac$_2$O, pyr
DMAP (94%)

16 R = H
16a R = Ac

8) 80% AcOH/H$_2$O
(97%)

9) Swern Oxidation
(96%)

10) DDQ, CH$_2$Cl$_2$:H$_2$O
(17:1, 87%)

11) NaClO$_2$ (9 equiv)
NaH$_2$PO$_4$ (8 equiv)
2-methyl-2-butene

17 R = MPM; X = H
18 R = H; X = H
19 R = H; X = OH

Finally, macrocyclization was achieved in 63% yield by the Yamaguchi procedure.[19] In situ generation of the mixed anhydride (2,4,6-trichlorobenzoyl chloride, ^{i}Pr$_2$NEt, DMAP, CH$_2$Cl$_2$) at 22 °C under high dilution conditions (0.0006 M for 18 h) yielded the fifteen-membered macrolactone ([α]^{23}$_D$ +76.1° (*c* 1.00, CHCl$_3$)). Removal of the C-9 allylic SEM ether was accomplished with mildly acidic conditions (PPTs, ^{t}BuOH, reflux), and transesterification (MeOH, K$_2$CO$_3$) yielded amphidinolide J (**1**) (58% for 2 steps). Comparisons of our synthetic amphidinolide J demonstrated that it was identical in all respects with spectroscopic data provided for the natural substance.[20]

Supporting Information Available: Experimental procedures and spectral data for all of the compounds of the synthesis pathway to (+)-amphidinolide J and ^{1}H/^{13}C NMR spectra of **1** (26 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(19) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. For a review of macrocyclization: Meng, W.; Hesse, M. *Top. Curr. Chem.* **1991**, 107−176.

(20) We thank Professor Jun'ichi Kobayashi (Hokkaido University) for providing proton and carbon NMR spectra of authentic **1**. Our synthetic **1** was also consistent with the published IR and MS data of the natural product.