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Total Synthesis of Amphidinolide J

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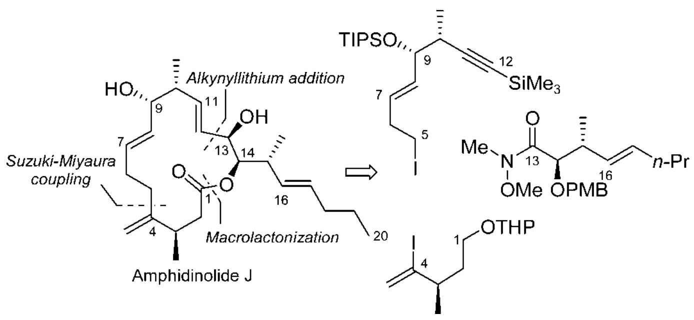
ABSTRACT



The marine natural product amphidinolide J has been synthesized according to a convergent strategy. The key steps of this synthesis include a *B*-alkyl Suzuki-Miyaura coupling and the addition of an alkynyllithium reagent to a Weinreb amide to build the C4−C5 and C12−C13 bonds, respectively, and a Yamaguchi macrolactonization.

The extracts from the marine dinoflagellate *Amphidinum* sp. have provided an impressive number of structurally diverse potent cytotoxic macrolides named amphidinolides.[1] Amphidinolide J, first isolated in 1993, is a 15-membered macrolactone polyketide bearing six stereocenters (C3, C9, C10, C13−C15), three disubstituted double bonds of *E* configuration (C7−C8, C11−C12, and C16−C17) as well as a methylene unit (at C4), which is a structural feature encountered in almost all amphidinolides.[2] Its absolute stereochemistry was ascertained by ozonolysis and stereoselective synthesis of the resulting degradation products.[2] Amphidinolide J exhibits cytotoxic activity against L1210 murine leukemia (IC$_{50}$ = 2.7 μg/mL) and KB human epidermoid carcinoma cells (IC$_{50}$ = 3.9 μg/mL).[2] In 1997, amphidinolides S and R, two minor congeners of amphidinolide J differing by the presence of a carbonyl group at C9 or from the size of the macrolactone (14-membered ring), were also isolated (Figure 1).[3]

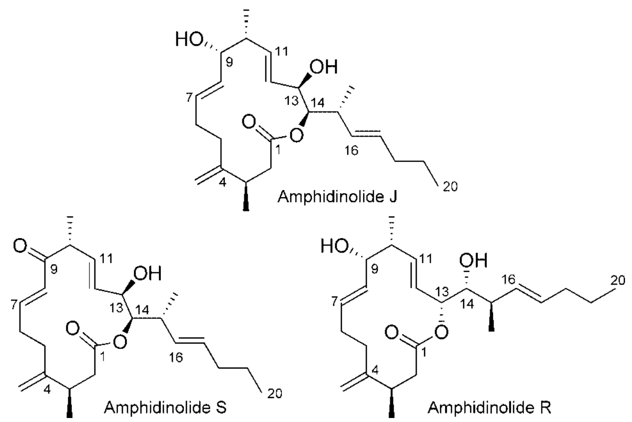


Figure 1. Structures of amphidinolides J, R, and S.

To date, only one total synthesis of amphidinolide J has been accomplished by Williams and Kissel in 1998[4] using a Negishi cross-coupling and a vinylzincate addition to an aldehyde to build the C6−C7 and C12−C13 bonds, respec-

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(1) (a) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93 (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451–460.

(2) Kobayashi, J.; Sato, M.; Ishibashi, M. *J. Org. Chem.* **1993**, *58*, 2645–2646.

(3) Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 7827–7832.

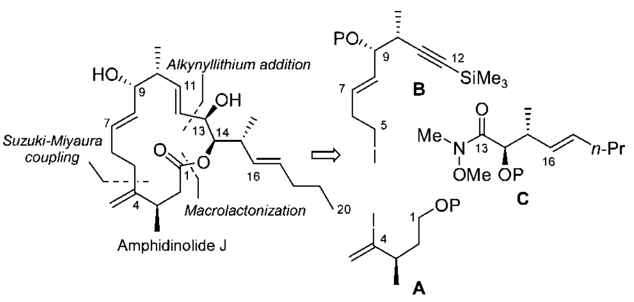
(4) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198–11199.

10.1021/ol801708x CCC: $40.75

tively, as well as a Yamaguchi macrolactonization. Herein, we would like to report a new convergent total synthesis of amphidinolide J and its formation from amphidinolide R by intramolecular transesterification.

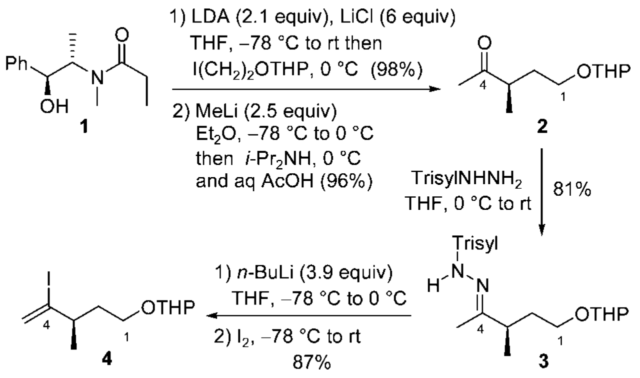
In our retrosynthetic analysis of amphidinolide J, the formation of the macrolactone was envisaged from a seco-acid which was disconnected at the C4−C5 and C12−C13 bonds. The formation of the C4−C5 bond would be achieved by a *B*-alkyl Suzuki-Miyaura cross-coupling between the alkenyl iodide **A** (C1−C4 subunit) and a boronate generated from the primary alkyl iodide **B** (C5−C12 subunit).[5] The C12−C13 bond would be created by the addition of an alkynyllithium reagent, generated from the alkynylsilane at C12, to the Weinreb amide **C** (C13−C20 subunit) (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Amphidinolide J



The synthesis of the C1−C4 fragment was first carried out. The lithium enolate generated from (1*S*,2*S*)-pseudoephedrine propionamide **1** underwent a diastereoselective alkylation with the THP ether derived from 2-iodoethanol and the resulting amide (98%, dr $\geq$ 95/5)[6,7] was subsequently converted to methyl ketone **2** by treatment with MeLi (96%). Ketone **2** was condensed with trisylhydrazide and trisylhydrazone **3** (81%) underwent a Shapiro reaction followed by iodinolysis of the alkenyllithium intermediate to afford alkenyl iodide **4** (87%). Thus, the C1−C4 subunit of amphidinolide J was prepared in four steps from amide **1**, in 66% overall yield (Scheme 2).

Scheme 2. Synthesis of the C1−C4 Subunit



The preparation of the C5−C12 fragment started with a cross-metathesis between homoallylic ether **5** and acrolein in the presence of Hoveyda−Grubbs catalyst **H-II** to provide the α,*β*-unsaturated aldehyde **6** (89%).[8] To introduce the two stereogenic centers at C9 and C10, aldehyde **6** was involved in an enantio- and diastereoselective crotyltitanation, with the (*E*)-crotyltitanium complex (*S*,*S*)-Ti-**I**, and homoallylic alcohol **7** (96%, ee = 92%, dr > 99/1) was obtained.[9,10] Protection of the secondary alcohol at C9 as a bulky triisopropylsilyl ether (96%) allowed a chemoselective dihydroxylation of the terminal alkene leading to the 1,2-diol **8** (72%, dr = 85/15).[11,12] After oxidative cleavage with $NaIO_4$, the resulting sensitive aldehyde was converted to the *gem*-dibromoolefin **9** (77%, two steps from **8**) and subsequent treatment with *n*-BuLi (THF, −78 °C), followed by silylation of the resulting alkynyllithium intermediate, provided alkynylsilane **10** (87%).[13] The alcohol at C5 was then deprotected[14] and converted to alkyl iodide **11** (92%).[15] The preparation of the C5−C12 fragment of amphidinolide J was therefore achieved in nine steps from homoallylic ether **5**, in 36% overall yield (Scheme 3).

The synthesis of the C13−C20 fragment was carried out from the acetylenic ketone **12**[16] which underwent enantioselective reduction catalyzed by ruthenium complex (*R*,*R*)-Ru-**II** in *i*-PrOH.[17] The corresponding propargylic alcohol (97%, ee = 95%)[18] was condensed with (4-methoxybenzyloxy)acetic acid (93%) followed by semihydrogenation of the triple bond to provide the (*Z*)-allylic glycolate **13** (93%). The latter compound was converted to the corresponding (*Z*)-silylketene acetal which underwent [3,3]-glycolate-Claisen rearrangement.[19] After hydrolysis, the resulting carboxylic acid was treated with trimethylsilyldia-

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(5) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

(6) Myers, A. G.; Yang, B. H.; Chen, H.; Mc Kinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

(7) The diastereoselectivity, with respect to the newly formed stereocenter (C3), could not be accurately evaluated because of the presence of the THP and amide rotamers. The ee of trisylhydrazone **3** was later checked (ee > 90%) by supercritical fluid chromatography, see Supporting Information.

(8) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (b) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *634*, 216–221.

(9) (a) Hafner, A.; Duthaler, R. O.; Mari, R.; Rihs, J.; Rothe-Streit, P.; Scharzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **1992**, 1595–1606.

(10) The ee of the homoallylic alcohol **7** was determined by supercritical fluid chromatography and comparison with a racemic sample prepared by addition of a crotylchromium reagent to aldehyde **6**.

(11) Andrus, M. B.; Lepore, S. D.; Sclafani, J. A. *Tetrahedron Lett.* **1997**, *38*, 4043–4046.

(12) Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* **2008**, *64*, 2495–2524.

(13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.

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(15) (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866–2869. (b) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473–1479.

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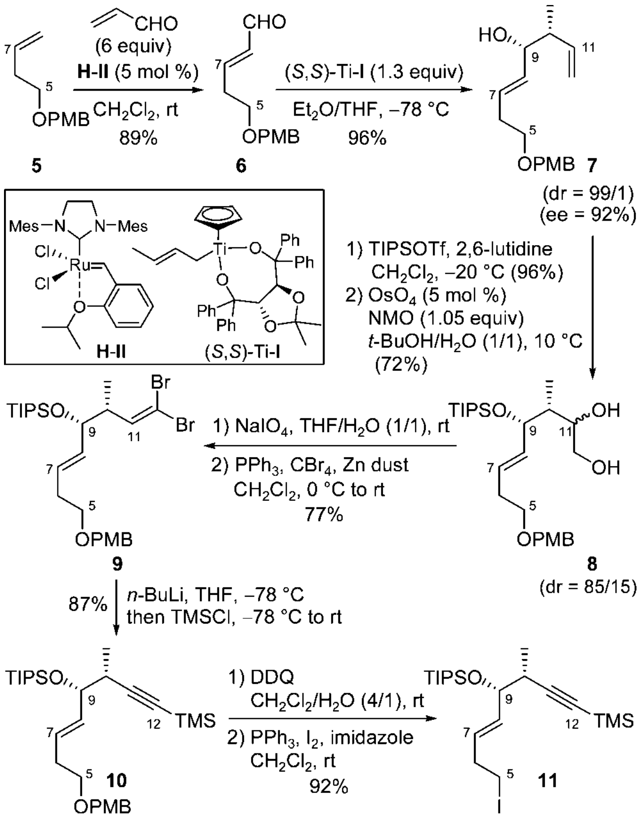
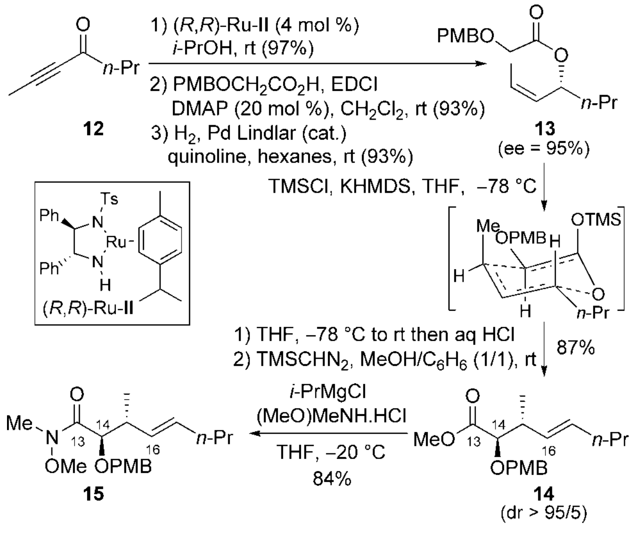
(17) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

(18) For the ee determination, see Supporting Information.

Scheme 3. Synthesis of the C5−C12 Subunit



Scheme 4. Synthesis of the C13−C20 Subunit



zomethane[20] and methyl ester **14** was obtained with high diastereoselectivity (87%, dr > 95/5) as a result of a chairlike transition state in which the propyl group preferentially occupies an equatorial position.[19] Methyl ester **14** was converted to Weinreb amide **15** (84%)[21] and the C13−C20 subunit of amphinidolide J was thus synthesized in six steps from ketone **12**, in 61% overall yield (Scheme 4).

Having synthesized the three subunits, their coupling was then studied. Alkyl iodide **11** was converted to a *B*-alkylboronate which underwent a palladium-catalyzed Suzuki−Miyaura coupling with the alkenyl iodide **4** to afford compound **16** in 82% yield.[5,22] After removal of the acetylenic TMS group (92%), the terminal alkyne was lithiated and condensed with Weinreb amide **15** to provide the acetylenic ketone **17** in quantitative yield.[23] To create the C13 stereocenter, ketone **17** underwent a diastereoselective reduction catalyzed by (*S*,*S*)-Ru-**II** (reagent-controlled),[17] and the resulting propargylic alcohol (96%, dr > 95/5) was hydroaluminated with Red-Al to afford the (*E*)-allylic alcohol **18** (84%). The secondary alcohol at C13 was protected as an acetate and the primary alcohol at C1 was deprotected by acid-catalyzed methanolysis. After oxidation with Dess−Martin periodinane and deprotection of the alcohol at C14, the seco-aldehyde **19** was obtained (83%, two steps from **18**). Oxidation of the aldehyde at C1 proceeded smoothly but afforded a mixture of two inseparable regioisomeric seco-acids **20** and **21** (4/1 ratio) due to partial migration of the acetyl group to the hydroxyl at C14 (Scheme 5).[24]

The crude mixture of seco-acids **20** and **21** was then subjected to macrolactonization under Yamaguchi conditions[25] to afford the 15-membered macrolactone **22** (34%) and the 14-membered macrolactone **23** (24%) which were readily separated by flash chromatography. Deprotection of the C9 hydroxyl group in compounds **22** and **23** led to macrolactones **24** (74%) and **25** (63%), respectively. The protecting acetyl group in the 15-membered macrolactone **24** was removed (K_2CO_3, MeOH, rt, 2 h) and amphidinolide J was isolated in 61% yield. Another fraction consisting of a 4/1 mixture of amphidinolides J and R was also isolated (15%). Interestingly, under similar conditions (rt, 4 h), an acyl shift took place from the 14-membered lactone **25** and amphidinolide J was again isolated as the major product (46%) along with a 1/1 mixture of amphidinolides J and R (18%) (Scheme 5).[26,27] The spectroscopic data of the isolated pure amphidinolide J were in perfect agreement with those

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(19) (a) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889–3901. (b) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221–5228.

(20) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478.

(21) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

(22) (a) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428–7432. For a recent application of those conditions, see: (b) Corbu, A.; Aquino, M.; Pratap, T. V.; Retailleau, P.; Arseniyadis, S. *Org. Lett.* **2008**, *10*, 1787–1790.

(23) An excess of alkynyllithium was used (2 equiv) and the terminal alkyne could be recovered (69% based on the unreacted reagent).

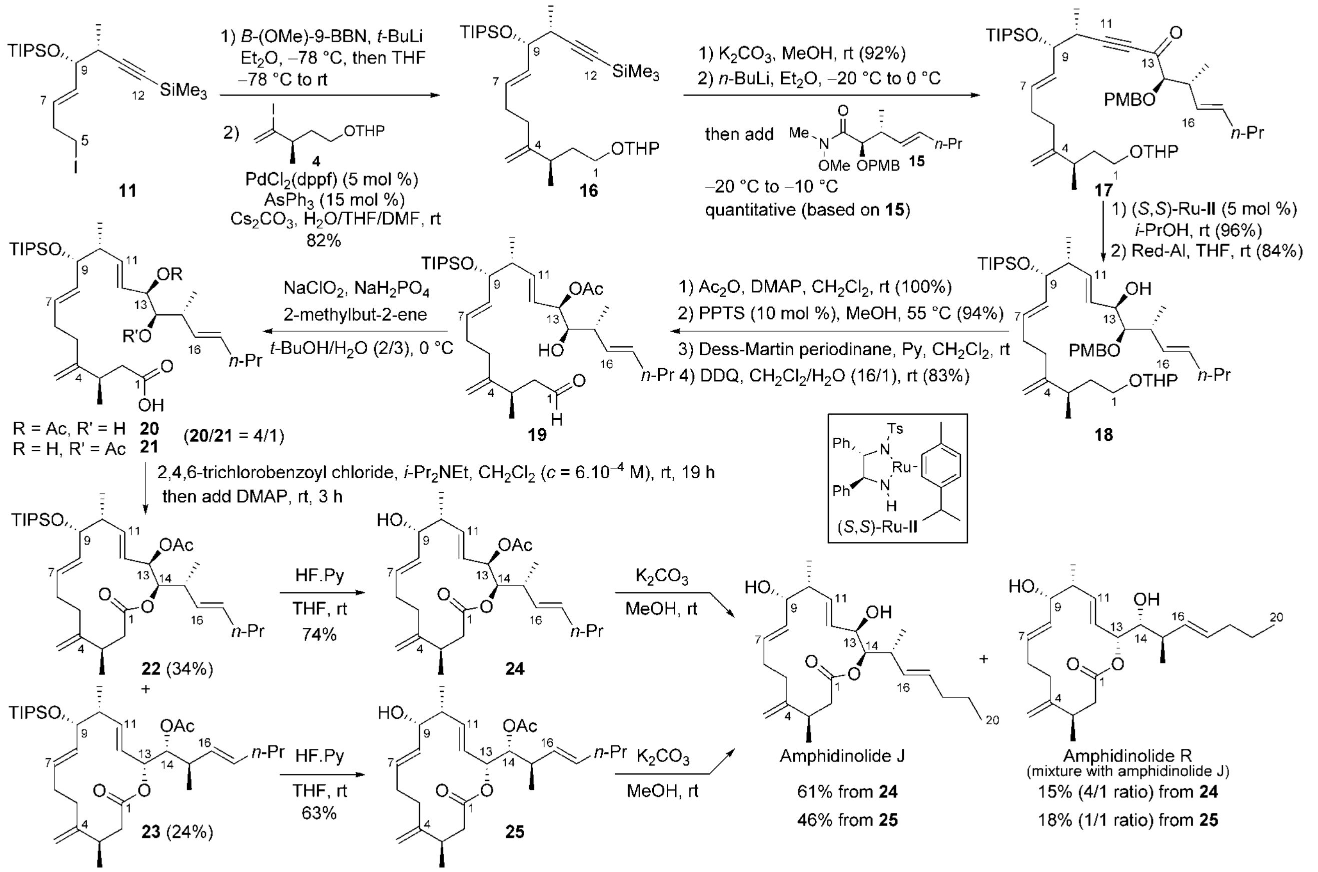
(24) Similar reaction conditions as described in ref 4 were used but transacetylation could not be avoided.

(25) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(26) For an example of translactonization from a 14- to a 15-membered ring, see: (a) Adachi, T. *J. Org. Chem.* **1989**, *54,* 3507–3510. Translactonization of a 15- to a 13-membered ring has been observed, see: (b) Sarabia, F.; Chammaa, S. *J. Org. Chem.* **2005**, *70*, 7846–7857.

(27) The reaction presumably proceeds under thermodynamic control but the use of longer reaction times resulted in the formation of byproducts presumably resulting from saponification, methanolysis, and/or degradation of the macrolactones.

Scheme 5. Total Synthesis of Amphidinolide J



previously reported for the natural product (Δδ ≤ 0.1 ppm in ^{1}H and ^{13}C NMR) with a measured optical rotation slightly higher ([α]$_D$ +6.7 (*c* 0.52, MeOH); lit[2] [α]$_D$ +1.2 (*c* 0.7, MeOH)).

In conclusion, we have reported a total synthesis of amphidinolide J in 22 steps (longest linear sequence) from homoallylic ether **5**, in 4% overall yield. A Myers alkylation, a Shapiro reaction, an enantioselective and diastereoselective crotyltitanation and a glycolate-Claisen rearrangement were utilized as key steps for the synthesis of the three subunits which were successively assembled by using a *B*-alkyl Suzuki−Miyaura cross-coupling (C4−C5 bond), the addition of an alkynyllithium to a Weinreb amide (C12−C13 bond), and a Yamaguchi macrolactonization.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR data for all compounds.This material is available free of charge via the Internet at http://pubs.acs.org.

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