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# Total Synthesis of Proposed Amphidinolide A via a Highly Selective Ring-Closing Metathesis

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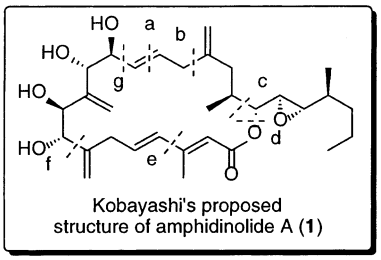
## ABSTRACT




key retrosynthetic disconnections
a: ring closing metathesis
b: indium mediated allylation
c: stereoselective anti-aldol
d: Mitsunobu esterification
e: Stille reaction
f-g: chelation controlled add'n

**A highly convergent synthesis of the proposed structure of amphidinolide A is reported. Instructive applications of several organometallic processes are illustrated, including a highly selective ring-closing metathesis reaction.**

Amphidinolide A was the first of a series of biologically active compounds isolated from the marine dinoflagellate *Amphidinolide* sp.[1] This molecule possesses marked biological activity against L1210 murine leukemia cells and rabbit skeletal muscle actomysion ATPase. Structurally, the 20-member macrolactone contains both lipophilic and hydrophilic moieties, as well as a series of conjugated and nonconjugated dienes. Driven in part by these intriguing features, several groups have targeted amphidinolide A for total synthesis.[2] Herein we describe our total synthesis of **1**, the proposed structure of amphidinolide A.

Retrosynthetic breakdown of **1** (Scheme 1) affords two major fragments **2** and **3**, which we planned to join by a Stille coupling between C3 and C4. The macrocyclic ring would be formed by a ring-closing metathesis (RCM) to generate the C13−C14 alkene. Given the array of olefinic functionality present in **1**, planning such a late stage RCM was not without obvious risks. Of particular concern would be the ability to control which alkenes underwent metathesis and the geometry of the resultant olefin. That said, a successful RCM-based route to **1** would be a noteworthy application of this very important methodology.[3]

Scheme 1 also illustrates deconstruction of Stille/RCM fragments **2** and **3**. Fragment **2** can be broken down into three components, **4**, **5**,[2c] and vinyl-MgBr. Chelation-controlled additions of the respective vinyl nucleophiles to aldehydes of D-arabitol-derived **4** would set the C8 and C12 stereocenters of the final target.

Fragment **3** could be formed by Mitsunobu esterifcation of **6**[4] with **7**. The decision to invert C19 during esterification was based on requirements for a stereocontrolled construction of fragment **7** (vide infra). In the synthesis of **7**, we planned to build the skipped diene using an In-mediated allylation of a terminal alkyne.

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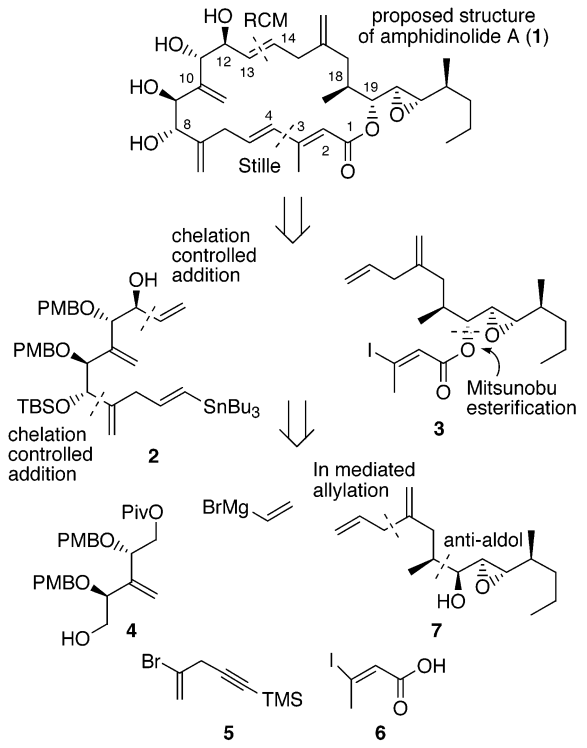
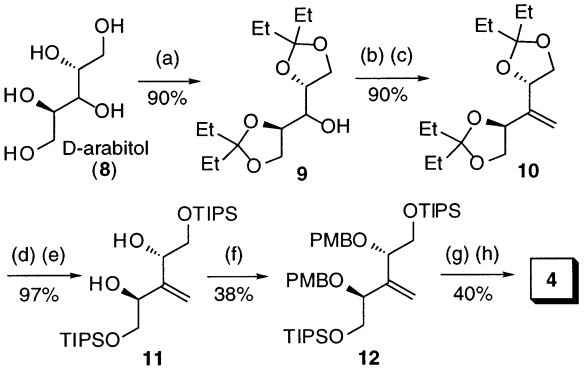
**Scheme 1**




The synthesis of **4** (Scheme 2) began with the conversion of D-arabitol (**8**) into diisopentylidene acetal **9**.[5] The remaining secondary alcohol was oxidized and subjected to a Wittig reaction, which effectively installed the exo olefin in **10**.

**Scheme 2**[a]



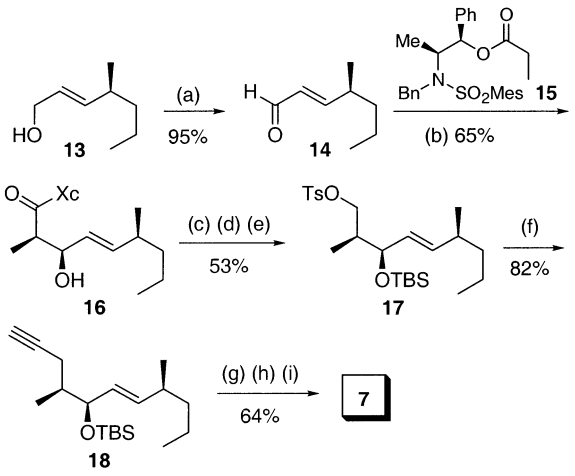

(a) 3,3-Dimethoxypentane, CSA, DMF, 38 °C, 90%. (b) $SO_3$·pyridine, DMSO, *i*-$Pr_2NEt$, rt, 1 h. (c) $Ph_3PCH_3Br$, NaHMDS, 0 °C → rt, then ketone, 0 °C, 4 h (90% from **9**). (d) CSA, $H_2O$, MeOH/$CH_2Cl_2$ (2:1), 40 °C, 7 h. (e) TIPSCl, imidazole, DMAP, DMF/$CH_2Cl_2$ (1:1), rt, 12 h (97% from **10**). (f) *p*-methoxybenzyl-2,2,2-trichloroacetimidate, CSA, 40 °C, 48 h, 38%. (g) TBAF, THF, 1.5 h. (h) PivCl, pyridine, $CH_2Cl_2$, 0 °C → rt, (40% from **12**).

Hydrolysis of the acetals with CSA was followed by selective protection of the primary alcohols as TIPS ethers to give **11**. The remaining alcohols were protected as PMB ethers to give the fully protected tetraol **12**. Removal of the TIPS groups with TBAF afforded a *C*-2 symmetric diol, which was then monoprotected as a pivalate to afford fragment **4**.[5]

During early studies, it became clear that to avoid a stereo mismatch[6] during a Sharpless installation of the epoxide in **7**, we would have to operate with C19 epimeric to that of the natural product. Such C19 stereochemistry along with the appropriate C18 methyl stereochemistry could be established by a stereoselective anti-aldol condensation.

Previously, we reported a chiral auxiliary based synthesis of allylic alcohol **13**.[2c] Chemical manganese dioxide (CMD)[7] proved to be an excellent heterogeneous oxidant for converting **13** into aldehyde **14** without need for chromatography (Scheme 3). With **14** in place, we began to experiment with anti-aldol conditions. After looking at various auxiliaries and procedures, we found that the Abiko−Masamune auxiliary (**15**) worked best, affording the anti-aldol product with high diastereoselectivity.[8] Transformation of aldol product **16** to primary tosylate **17** allowed for introduction of an acetylene unit by nucleophilic displacement. Indium-mediated Markovnikov addition of an allyl group to alkyne **18** installed the skipped diene.[9] Deprotection and Sharpless epoxidation

**Scheme 3**[a]




(a) CMD, $CH_2Cl_2$, rt, 16−24 h, 95%. (b) **15,** $Cy_2BOTf$, TEA, −78 °C, 2 h, then **14**, −78 → −60 °C, 16 h, MeOH, pH 7 buffer, $H_2O_2$ 0 °C → rt, 65%. (c) TBSOTf, 2,6-lutidene, 0 °C, 94%. (d) DIBAL, $CH_2Cl_2$, −78 °C, 2 h, 83%. (e) TsCl, TEA, $CH_2Cl_2$, 0 °C, 20 min, rt, 16 h, 68%. (f) lithium acetylide ethylenediamine complex, DMSO, 16 h, 82%. (g) allyl bromide, cut indium rod, THF, sonication, 42 °C, 6 h, 80%. (h) TBAF, 0.5 equiv HOAc, THF, rt → 40 °C, 89%. (i) Ti(*i*-PrO)$_4$, L-diethyl tartrate, *t*-BuOOH, 4 Å sieves, $CH_2Cl_2$, −23 °C, 24 h, 89%.

(5) The structure assigned to each new compound used in the synthesis of **1** is in accord with its IR, $^1H$ NMR, $^{13}C$ NMR, and HRMS spectral data. See Supporting Information for key details.

(6) Pfenninger, A. *Synthesis* **1986**, 89−116.

(7) Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35−36.

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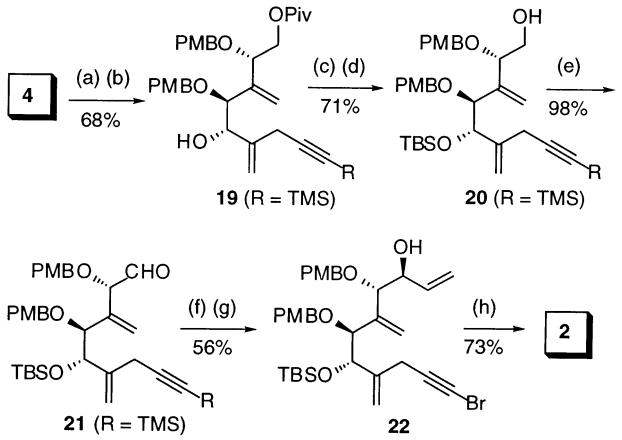
occurred smoothly on the matched allylic alcohol to afford **7**[5] as a single observable isomer.

With **4** and **7** prepared and fragments **5**[2c] and **6**[4] known, final assembly of **1** could begin. Dess−Martin oxidation of fragment **4** gave a pseudosymmetric aldehyde. This afforded us the option of introducing either alkene **5** or the northern vinyl group first. In theory, we preferred to add the commercially available vinyl-MgBr early and our synthetic material late. However, in practice, chelation-controlled addition of the Grignard reagent derived from **5** proved best, affording **19** as a single diastereomer (Scheme 4). In contrast,

**Scheme 4**[a]




(a) DMP, pyridine, $CH_2Cl_2$, 98%. (b) **5**, *t*-BuLi, $Et_2O$, −78 °C, then added $MgBr_2{\cdot}Et_2O$ in $Et_2O$/PhH (3:1), −78 °C → rt, 25 min, then aldehyde + $MgBr_2{\cdot}Et_2O$ in $CH_2Cl_2/Et_2O$/PhH, 0 °C, 45 min, 70%. (c) TBSOTf, 2,6-lutidene, $CH_2Cl_2$, 0 °C, 30 min, 81%. (d) Super-Hydride, THF, 0 °C, 35 min, glycerol workup, 88%. (e) DMP, pyridine, 1.5 h, rt, 98%. (f) **21** + $MgBr_2{\cdot}Et_2O$ in $CH_2Cl_2/Et_2O$/PhH, vinyl-MgBr in THF, 1 h, 0 °C, 60% (7:1). (g) NBS, $AgNO_3$, acetone, rt, 92%. (h) $Bu_3SnF$, Red-Sil, $(Ph_3P)_2PdCl_2$, cat. TBAF, $Et_2O$, rt, 2.5 h, 73%.

adding vinyl-MgBr to the same aldehyde gave a mixture of products. Protective group manipulation and oxidation of **19** afforded **21**. Fortunately, chelation-controlled addition of vinylmagnesium bromide to this aldehyde proved reasonably efficient, affording a 7:1 mixture of epimers at what would become C12 in the final target. Because placement of a bromide at the terminal position of an alkyne provides a good regiocontrol handle[10] for Pd(0)-mediated hydrostannations, the acetylenic TMS group was reacted with NBS to afford **22**. $Bu_3SnH$ for the hydrostannation was generated in situ[11] with $Bu_3SnF$, catalytic TBAF, and Red-Sil (silane capped silica gel).[12] Compared to the direct employment of $Bu_3SnH$, this in situ method afforded **2**[5] in superior yield and geometric purity. Furthermore, as all spent reagents were salts, **2** could be purified by passage through a plug of silica gel, thereby minimizing any chance of destannylation.

Fragment **3** now needed to be prepared. Despite the presence of the possibly reactive epoxide, Mitsunobu esterifcation of **6** and **7** provided fragment **3**[5] in good yield. We were now ready to investigate the final intermolecular union. Though conventional Stille coupling[13] of **2** and **3** worked fine (60% yield), substitution of stoichiometric Cu(I) thiophene carboxylate (Liebeskind's conditions) for catalytic Pd(0) afforded diene **23** in significantly less reaction time (30 min vs 18 h).[14]

The stage was now set to study the key RCM step. We initially hypothesized that by using the less reactive first-generation Grubbs' catalyst, the greater reactivity of monosubstituted alkenes could be exploited and a selective C13−C14 metathesis achieved.[15] Unfortunately this catalyst only truncated the allylic alcohol to give the methyl ketone.[16] That problem was virtually eliminated by using the imidazolium-based catalyst,[3b] and more importantly, we achieved the desired RCM. Though metathesis occurred in only moderate yield and required high catalyst loading (50 mol %), no other RCM products were detected and to our delight only the C13−C14 *E*-isomer of **24** was observed.[5]

Attempts at removing the PMB groups on **24** were complicated by formation of PMB-derived acetals with the C12 hydroxyl. Thus the free OH of **24** was protected as a TBS ether (Scheme 5), before removal of the PMB groups by buffered DDQ oxidation. The two TBS groups were then removed using TBAF buffered with HOAc to afford presumed amphidinolide A (**1**). However, NMR data from our synthetic material did not match those of the natural product, primarily in the chemical shifts of protons at C4, C8, C9, C11, C13, C17, and C19.[5] Optical rotation of our material (−56) also differed from the natural product (+46) in magnitude and sign.

Assigning the structure of **1** on spectral data alone is difficult. The diffierence between the synthetic and natural products could be the result of a misassignment made during our synthesis or during isolation of the natural product.[17] Therefore, we set out to (a) secure the structure of our synthetic material by single crystal analysis and (b) synthetically explore the possibility that Kobayashi misinterpreted his spectral data.

Because the two stereochemical containing regions of **1** (C8−C12 and C18−C22) are separated, we hypothesized that the original correlation of these two halves may have been wrong. Starting with L-arabitol we constructed mac-

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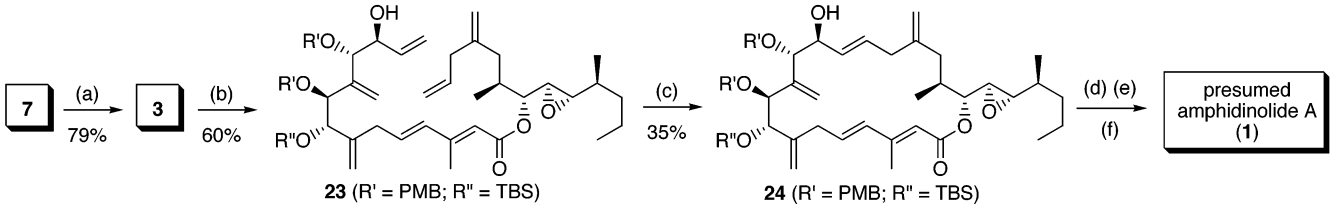
(17) Comparisons to the natural product are complicated by the existence of only a TLC sample of natural amphidinolide A. Kobayashi, J., Hokkaido University, personal communication, 2000.

**Scheme 5**[a]




(a) DIAD, $Ph_3P$, **6**, THF, 0 °C 30 min, rt, 16 h, 79%. (b) **2**, Cu(I) thiophenecarboxylate, NMP, 0 °C → rt, 45 min, 60%. (c) PhHC═Ru($PCy_3$)(IMes-$H_2$)$Cl_2$ (50 mol %), $CH_2Cl_2$, 40 °C, 24 h, 35%. (d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 75 min, 92%. (e) DDQ, *t*-BuOH/pH 7 buffer/$CH_2Cl_2$ (1:1:5), 4 h, rt, 52%. (f) TBAF, HOAc, THF, rt, 21 h, 25%.

rocycle **25** (Figure 1), which is epimeric to **1** at C8, C9, C11, and C12. If our theory concerning the correlation of the two halves held, **25** would be either the natural product or its

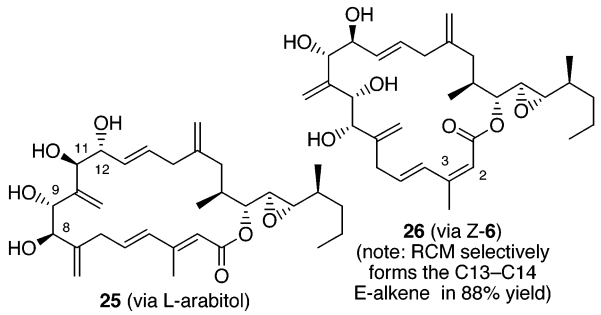



**Figure 1.** Amphidinolide A analogues.

enantiomer. Unfortunately, $^1$H NMR data pointed to **25** being a diastereomer of amphidinolide A.[18] We also applied our synthetic strategy to the synthesis of C2−C3 "*Z*-amphidinolide A" (**26**). While $^1$H NMR analysis also established **26** as a diastereomer of the natural product, its synthesis highlights the potential of an RCM approach to polyene macrocycles, as the RCM leading to **26** occurred with only 20 mol % catalyst in 88% yield and with complete *E*-selectivity.[18]

In the midst of our attempts to obtain X-ray diffraction data on the synthetic material, Pattenden and co-workers published their route to **1**.[2a] Spectral and optical data for their final compound matched ours and not Kobayashi's.

(18) Details, including biological data, to be reported elsewhere.

Pattenden's route differs from our approach in that (a) their synthesis of the tetraol region starts with D-glucose and employs different protective groups, (b) their esterification does not invert C19, and (c) they close the macrocycle via Pattenden's $sp^2-sp^3$ coupling method.[2e] Given these differences, there is little chance of a common erroneous step corrupting the spectral and optical data in exactly the same way. Thus, despite the lack of crystallographic data, the two independent routes to **1** affirm both group's assignment of presumed amphidinolide A to our final products and confirm that the structure of the natural product needs to be revised.

In summary, we have synthesized presumed amphidinolide A (**1**) and analogues **25** and **26**. Our syntheses consist of 35 steps from articles of commerce with the longest linear sequence being 23 steps from L-(−)-ephedrine. Highlights of this work include instructional applications of several organometallic methods and unprecedented selectivity in the formation of a polyolefinic macrocycle by ring-closing metathesis.

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**Supporting Information Available:** Spectral data for key fragments **2**−**5**, and **7**, as well as final targets **1**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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